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(54) Title: SUBSTITUTED N-[(AMINOIMINOMETHYL OR AMINOMETHYL)PHENYL]PROPYL AMIDES

(57) Abstract

The compounds according to the invention are substituted N-[(aminoiminomethyl or aminomethyl)phenyl]propyl amides of formula (I) herein which exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are Factor Xa inhibitors. The present invention is directed to compounds of formula (I), compositions containing compounds of formula (I), methods for their preparation and their use, which are for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.

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SUBSTITUTED N-[(AMINOIMINOMETHYL OR AMINOMETHYL)PHENYL]PROPYL AMIDES

Field of the Invention

The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are Factor Xa inhibitors. The present invention is directed to compounds of formula I, compositions containing compounds of formula I, and their use, which are for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.

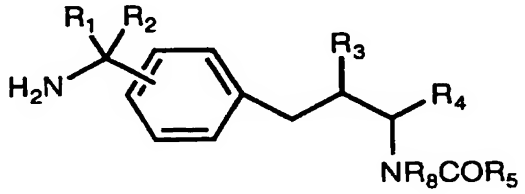
Factor Xa is the penultimate enzyme in the coagulation cascade. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula I. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal

coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

SUMMARY OF THE INVENTION

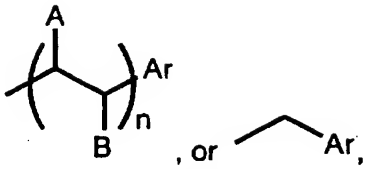
This invention is directed to the pharmaceutical use of a compound of formula I below to inhibit the production or physiological effects of Factor Xa in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of Factor Xa, where formula I is as follows:



R_1 and R_2 are hydrogen or taken together are $=NR_9$;

R_3 is $-CO_2R_6$, $-C(O)R_6$, $-CONR_6R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

R_4 is a group of formula



or R_4 is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl;

R_5 is alkyl, alkenyl, optionally substituted aryl or optionally substituted heteroaryl;

R_6 is hydrogen or lower alkyl;

R_7 is hydrogen, lower alkyl, lower acyl, aroyl or heteroaryl;

R_8 is hydrogen or lower alkyl;

R_9 is wherein R_9 is $R_{10}O_2C$-, $R_{10}O$-, HO-, cyano, $R_{10}CO$-, HCO-, lower alkyl, nitro, or Y^1Y^2N-, where R_{10} is optionally substituted alkyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl, and where Y^1 and Y^2 are independently hydrogen or alkyl;

A and B are hydrogen or taken together are a bond;

Ar is optionally substituted aryl or optionally substituted heteroaryl; and

n is 0, 1 or 2; or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more halo, cycloalkyl or cycloalkenyl. Exemplary alkyl groups include methyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more halo. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl and decenyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopentyl, fluorocyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group may be substituted by one or more halo, methylene (H_2C=) or alkyl. Exemplary multicyclic cycloalkyl rings include 1-decalin, adamant-(1- or 2-)yl and norbornyl.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. An exemplary multicyclic

cycloalkenyl ring is norbornylenyl. The cycloalkenyl group may be substituted by one or more halo, methylene (H_2C=) or alkyl.

"Heterocylyl" means a non-aromatic monocyclic or multicyclic ring system of about 3 to about 10 ring atoms. Preferred rings include about 5 to about 6 ring atoms wherein one of the ring atoms is oxygen, nitrogen or sulfur. The heterocyclyl may be optionally substituted by one or more halo. Preferred monocyclic heterocyclyl rings include pyrrole, tetrahydrothiophenyl and tetrahydrothiopyranyl. The thio or nitrogen moiety of the hetercyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aryl" means aromatic carbocyclic radical containing about 6 to about 10 carbon atoms. Exemplary aryl include phenyl or naphthyl optionally substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes hydrogen, alkyl, optionally substituted aryl, optionally substituted heteroaryl, aralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, carboxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, aralkylthio, Y^1Y^2N-, Y^1Y^2N-, Y^1Y^2N-alkyl-, CO- or $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl. Preferred aryl group substituents include hydrogen, alkyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently hydrogen and alkyl.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. The "heteroaryl" may also be substituted by one or more aryl group substituents. Exemplary heteroaryl groups include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, quinolinyl, indolyl, and isoquinolinyl.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the alkyl group is as previously described. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl groups is as previously described. Exemplary aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. An exemplary aralkylthio group is benzylthio.

"Y^1Y^2N-" means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as previously described. Exemplary groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Y^1Y^2NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are carbamoyl (H_2NCO-) and dimethylaminocarbamoyl (Me_2NCO-).

"$Y^1Y^2NSO_2$-" means a substituted or unsubstituted sulfamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are aminosulfamoyl (H_2NSO_2-) and dimethylaminosulfamoyl (Me_2NSO_2-).

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

"Alkylsulfonyl" means an alkyl-SO_2- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an aryl-SO_2- group.

"Arylsulfinyl" means an aryl-SO- group.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Pro-drug" means a compound which may or may not itself be biologically active but which may, by metabolic, solvolytic, or other physiological means be converted to a biologically active chemical entity.

Preferred Embodiments

A preferred embodiment of the invention is a method for treating a disease state capable of being modulated by inhibiting production of Factor Xa to a patient suffering from said disease state an effective amount of the compound of formula I .

A preferred compound aspect of the invention is the compound of formula I wherein R_1 and R_2 taken together are =NH.

Another preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CO_2R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

Another preferred compound aspect of the invention is the compound of formula I wherein n is 1.

Another preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CO_2R_6$ and R_6 is lower alkyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CH_2OR_7$ or $-CH_2SR_7$ and R_7 is hydrogen or lower alkyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_1 and R_2 taken together are =NH and form an aminoiminomethyl on the phenyl moiety that is in the meta position to the position of attachment of the phenyl moiety to the propyl moiety.

Another preferred compound aspect of the invention is the compound of formula I wherein Ar is optionally substituted aryl.

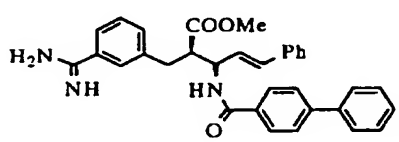
Another preferred compound aspect of the invention is the compound of formula I wherein Ar is phenyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_5 is optionally substituted phenyl, optionally substituted biphenyl, optionally substituted naphthyl, or optionally substituted heterobiphenyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_{10} is lower alkyl.

Included within the scope of formula I are compounds wherein R_1 and R_2 taken together are $=NR_9$, wherein R_9 is $R_{10}O_2C$-, $R_{10}O$-, cyano, $R_{10}CO$-, optionally substituted lower alkyl, nitro, or Y^1Y^2N-. Such derivatives may themselves comprise the biologically active compound useful for treating a disease state capable of being modulated by inhibiting production of Factor Xa to a patient suffering from said disease state, or may act as pro-drugs to such biologically active compounds which are formed therefrom under physiological conditions.

Species according to the invention are selected from the following:



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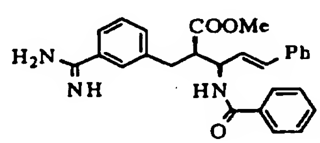

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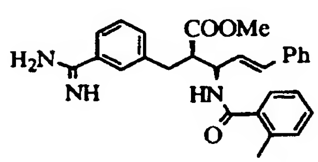

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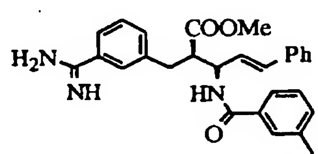

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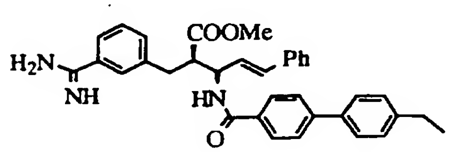

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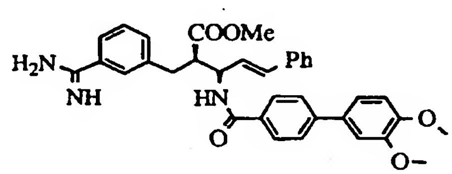

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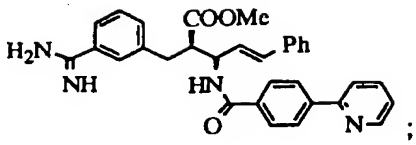
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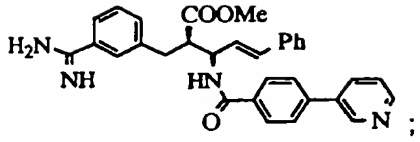
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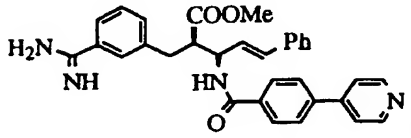
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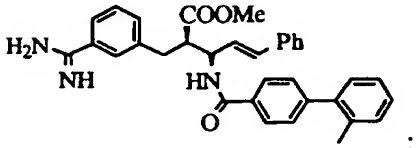
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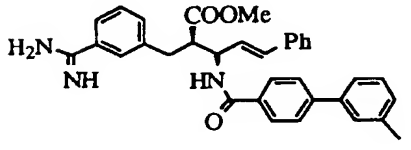
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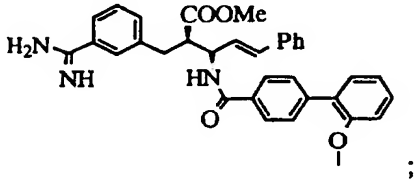
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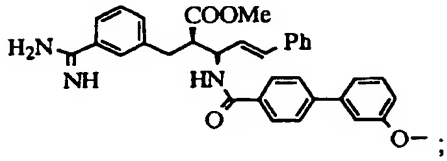
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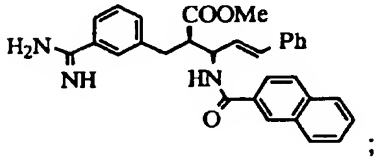
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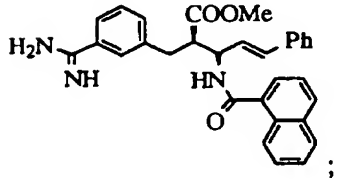
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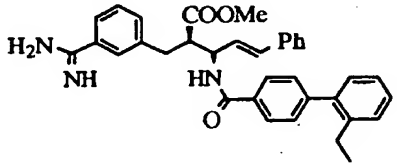
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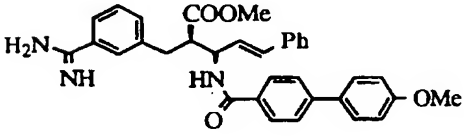
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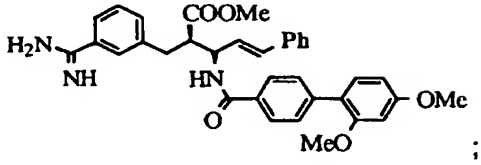
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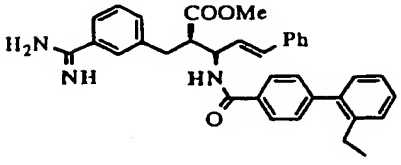
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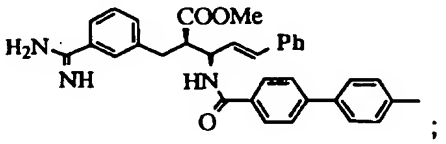
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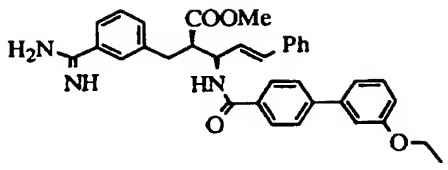
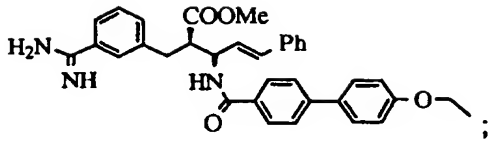

COOMe
Ph
H_2N
NH
HN
O
O
;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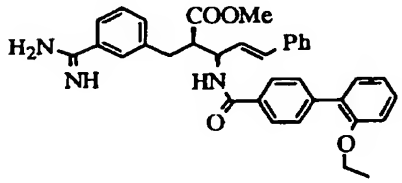
Ph
H_2N
NH
HN
O
O
;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Ph
H_2N
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HN
O
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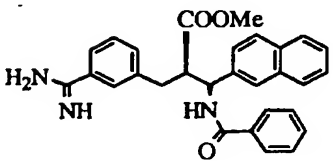
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H_2N
NH
HN
O
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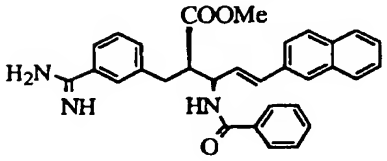
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H_2N
NH
HN
O
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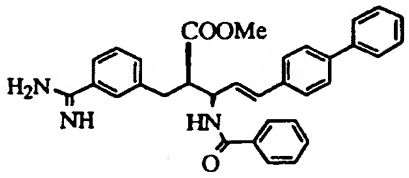
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H_2N
NH
HN
O
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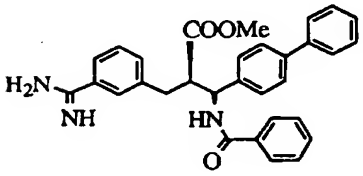
COOMe
H_2N
NH
HN
O
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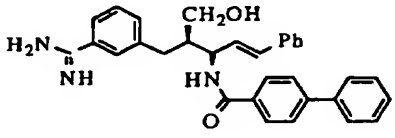
CH_2OH
Pb
H_2N
NH
HN
O
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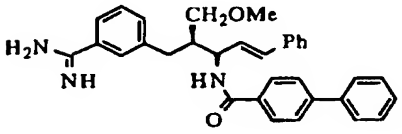
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Ph
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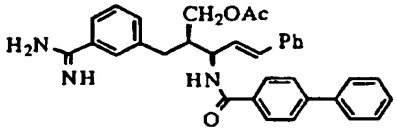
NH
HN
O
;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NH
HN
O
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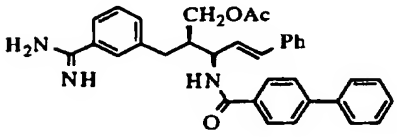
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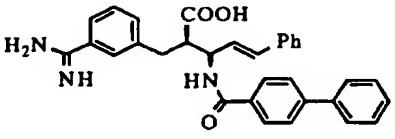
Ph
H_2N
NH
HN
O
;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Ph
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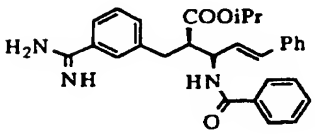
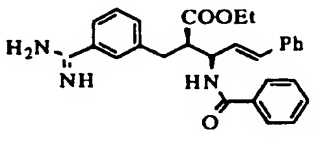
NH
HN
O
;


COOiPr
Ph
H_2N
NH
HN
O
;


COOEt
Ph
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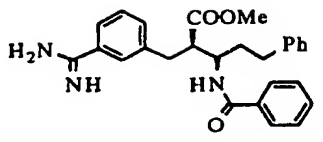
NH
HN
O
;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NH
HN
O
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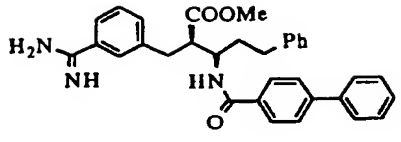
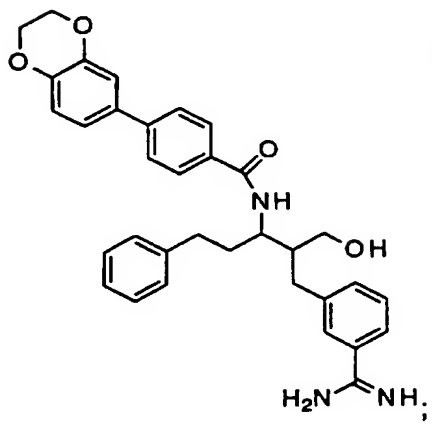

COOMe
Ph
H_2N
NH
HN
O
;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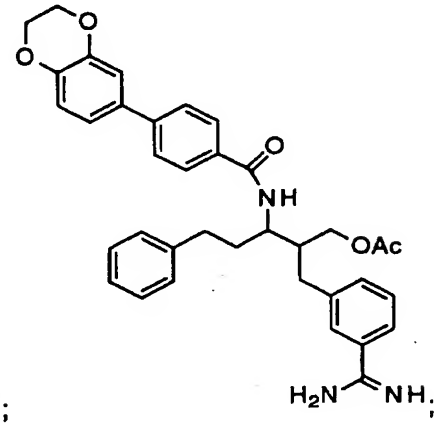
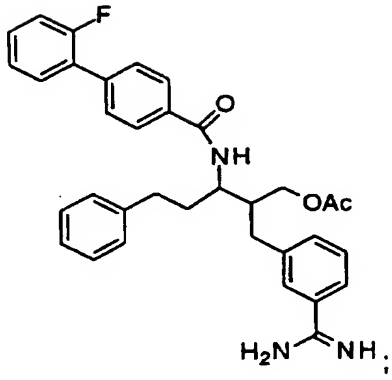
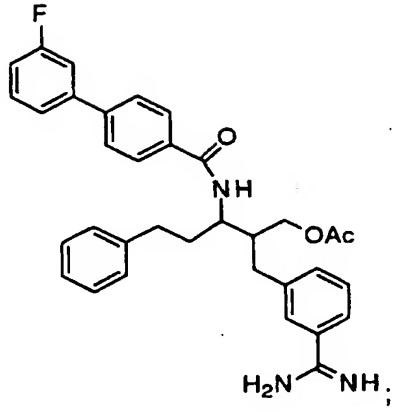
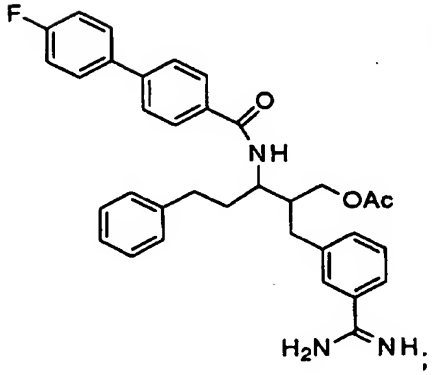
O
NH
OH
H_2N
NH
;


O
O
NH
OAc
H_2N
NH
;


F
O
NH
OAc
H_2N
NH
;


F
O
NH
OAc
H_2N
NH
;

5


F
O
NH
OAc
H_2N
NH
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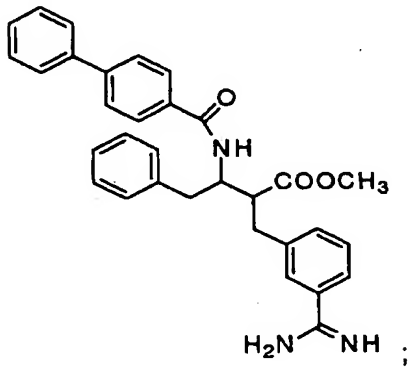
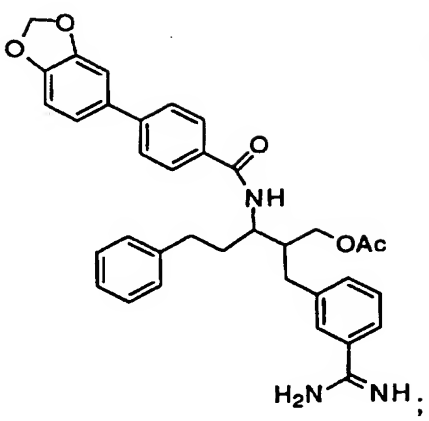
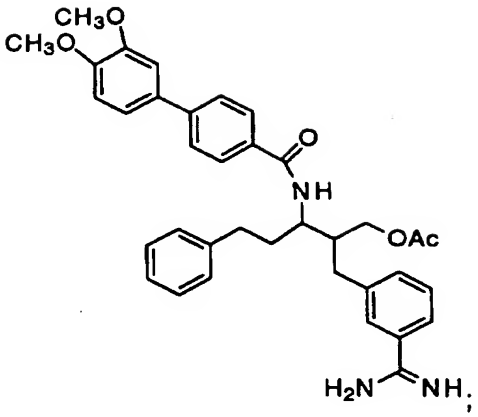
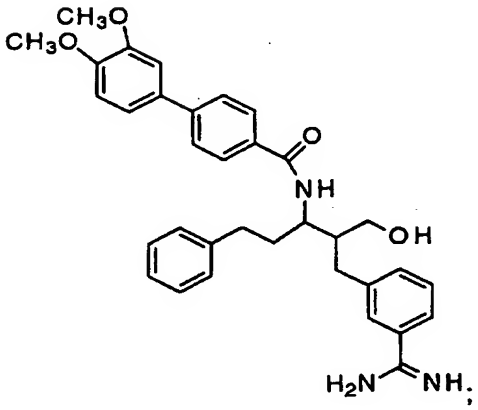
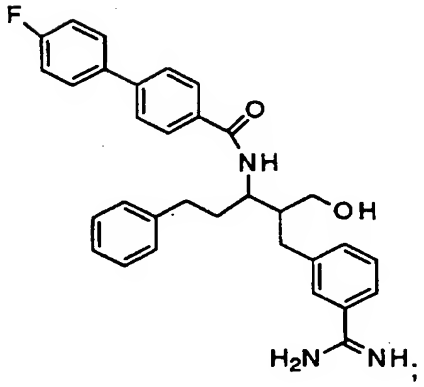
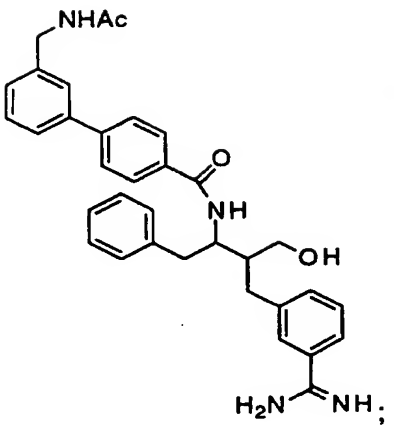

O
NH
$COOCH_3$
H_2N
NH
;

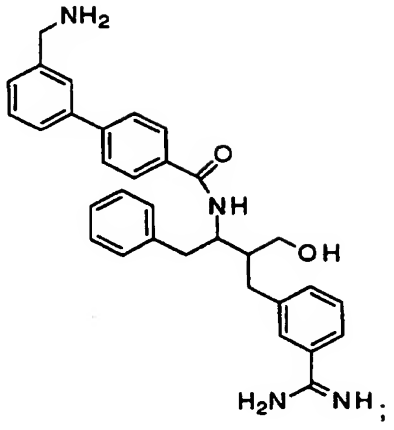












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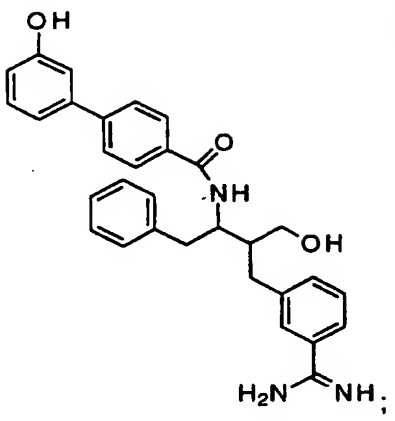

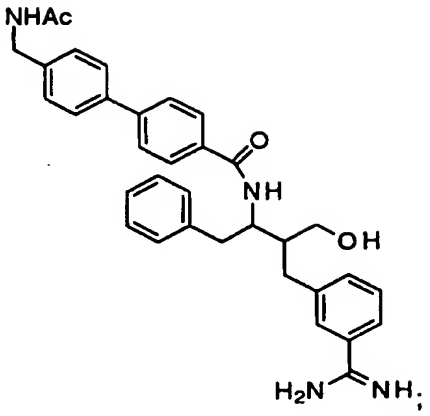

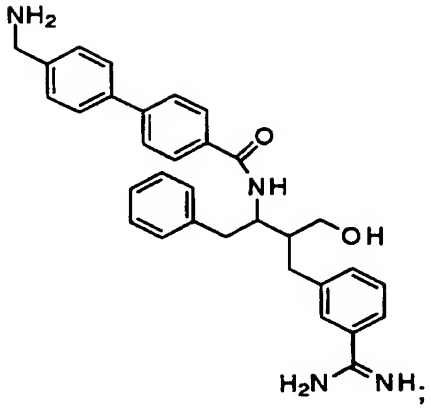

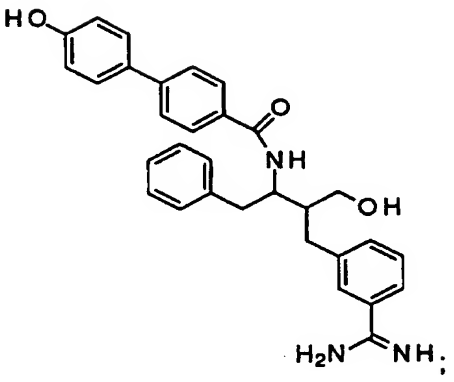

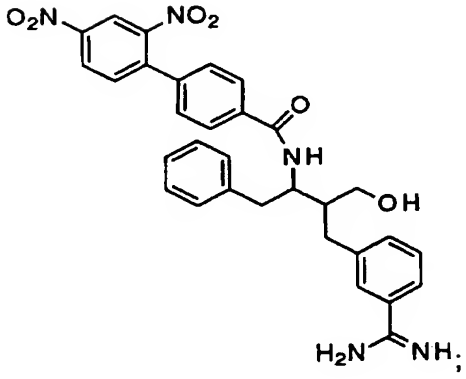

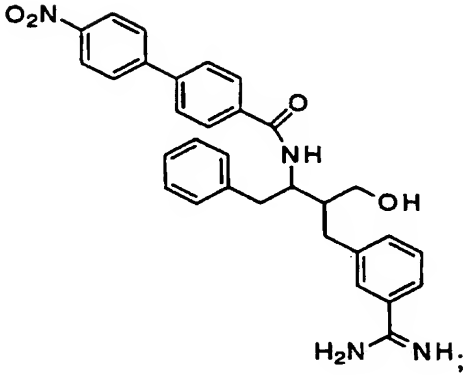

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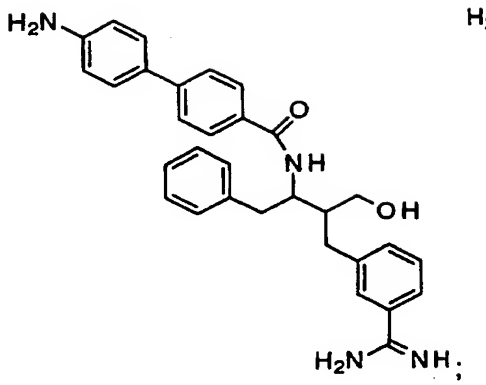

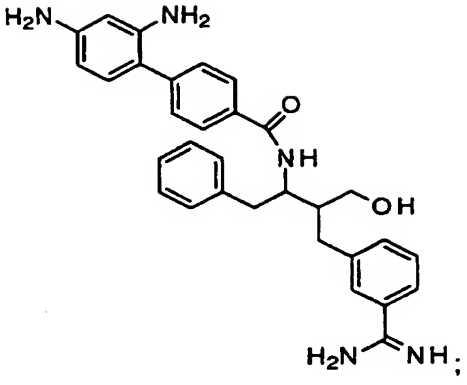

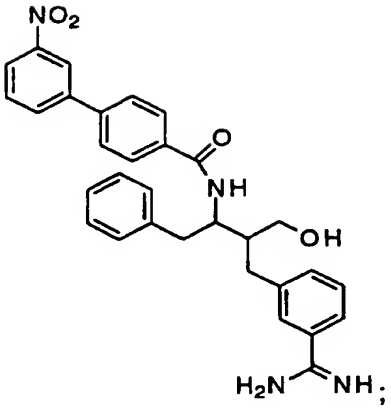

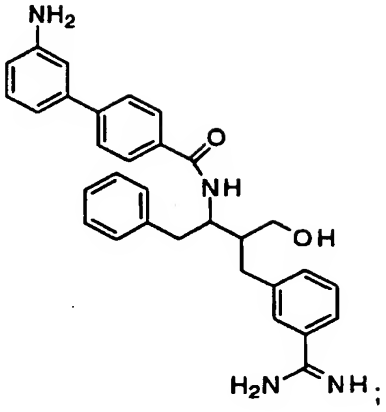

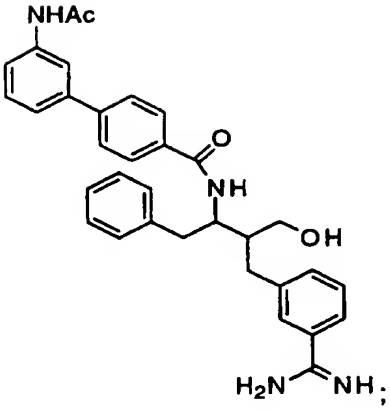

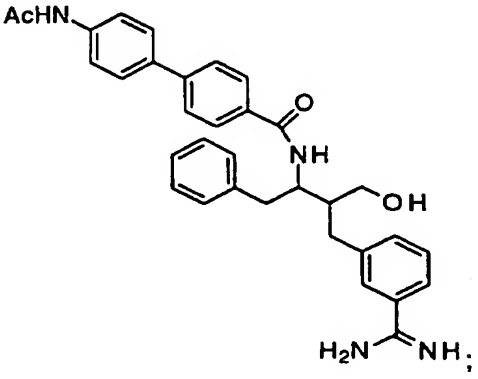

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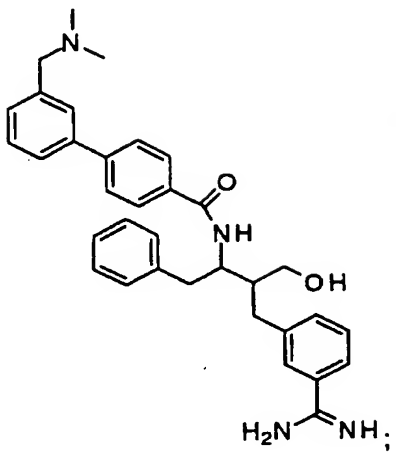

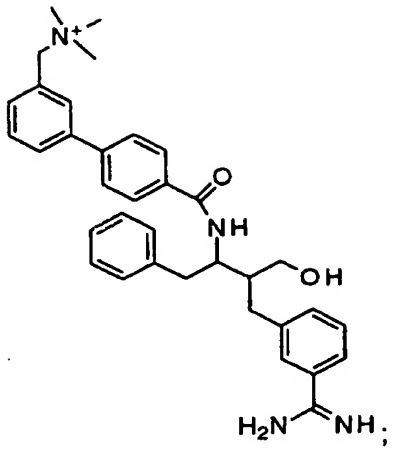

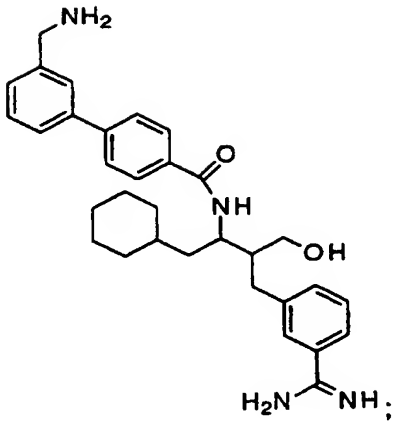

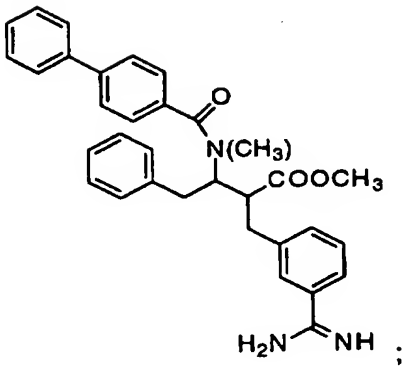

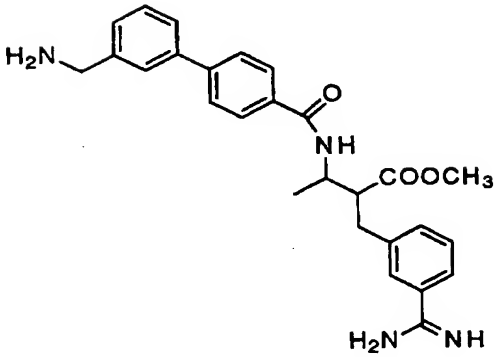

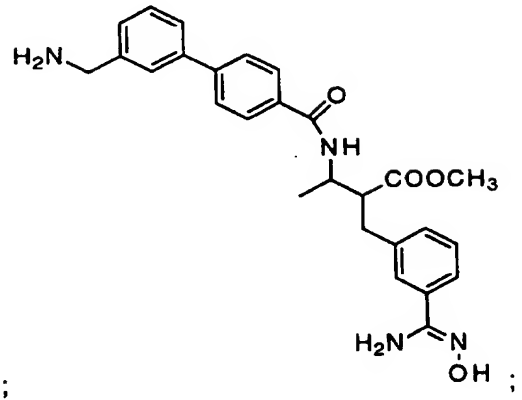

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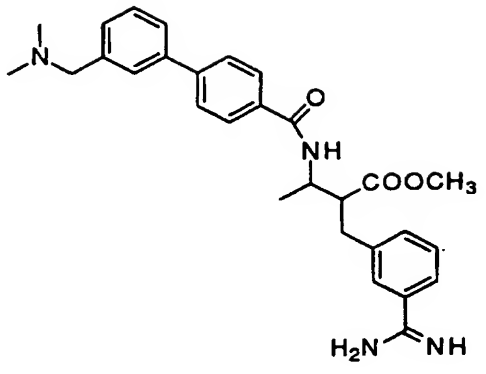
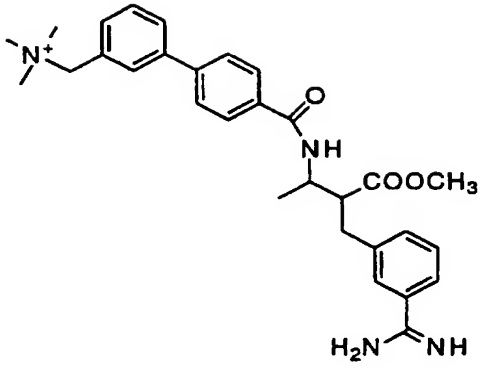
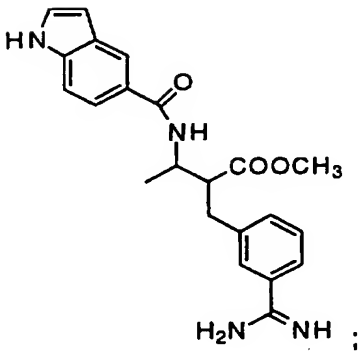

N
O
NH
COOCH3
H2N
NH

;


N+
O
NH
COOCH3
H2N
NH

;


HN
O
NH
COOCH3
H2N
NH

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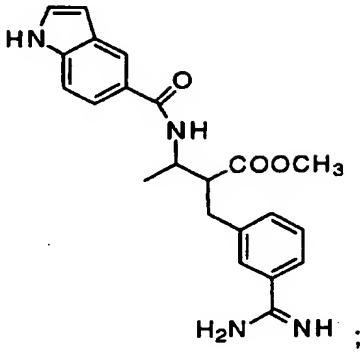
HN
O
NH
COOCH3
H2N
NH

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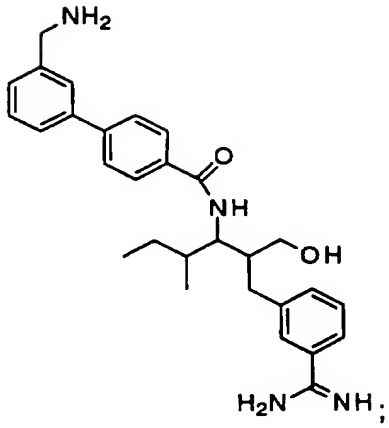
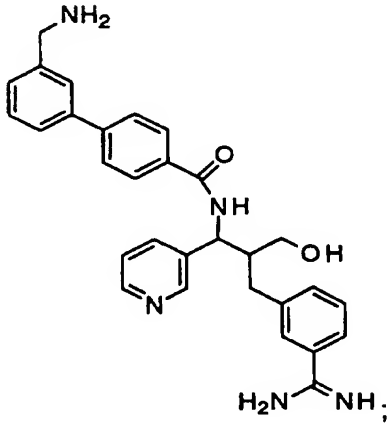
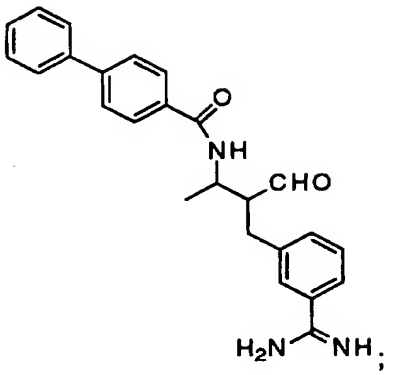

NH2
O
NH
OH
H2N
NH

;


NH2
O
NH
OH
N
H2N
NH

;

5



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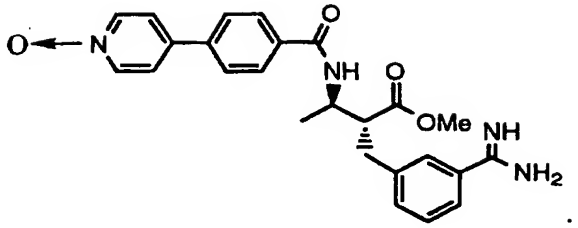

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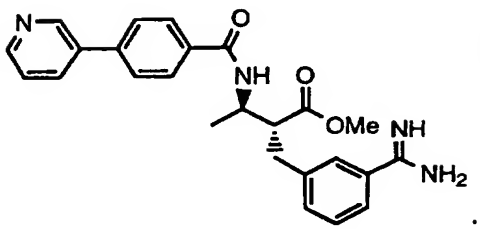

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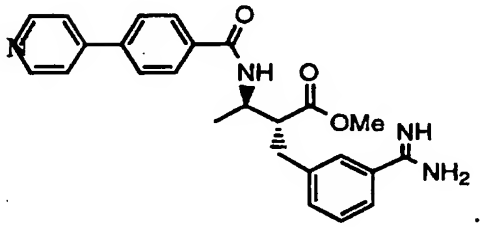

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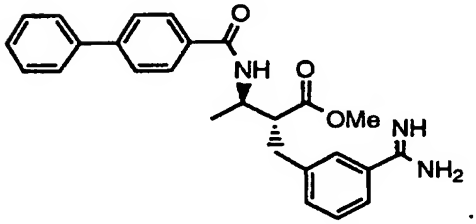

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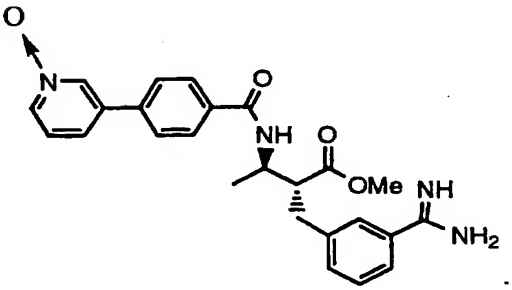

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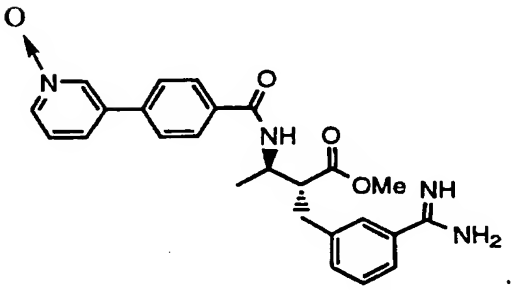

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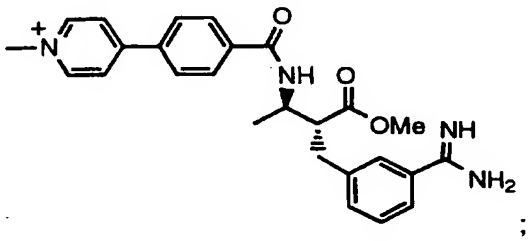

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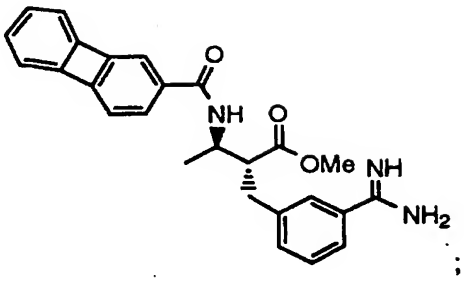
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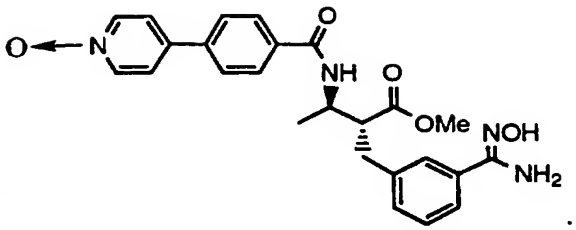
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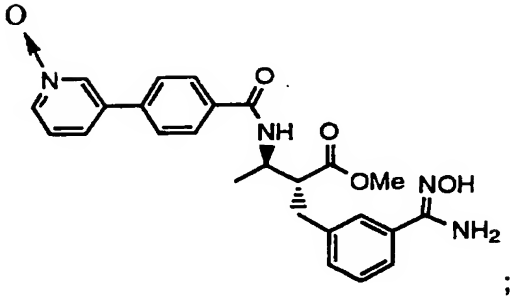
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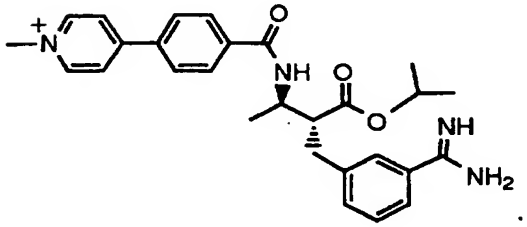
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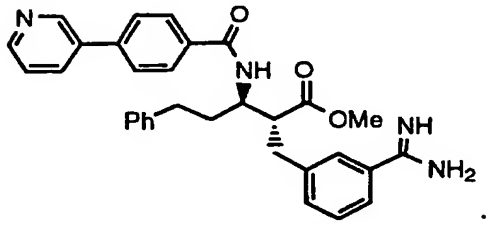
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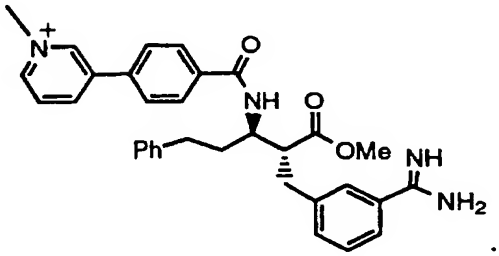
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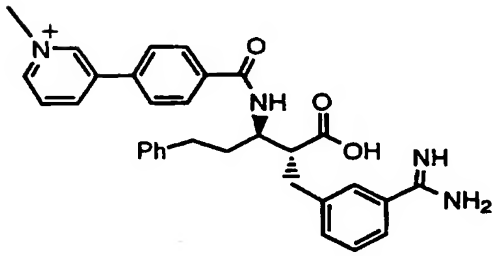
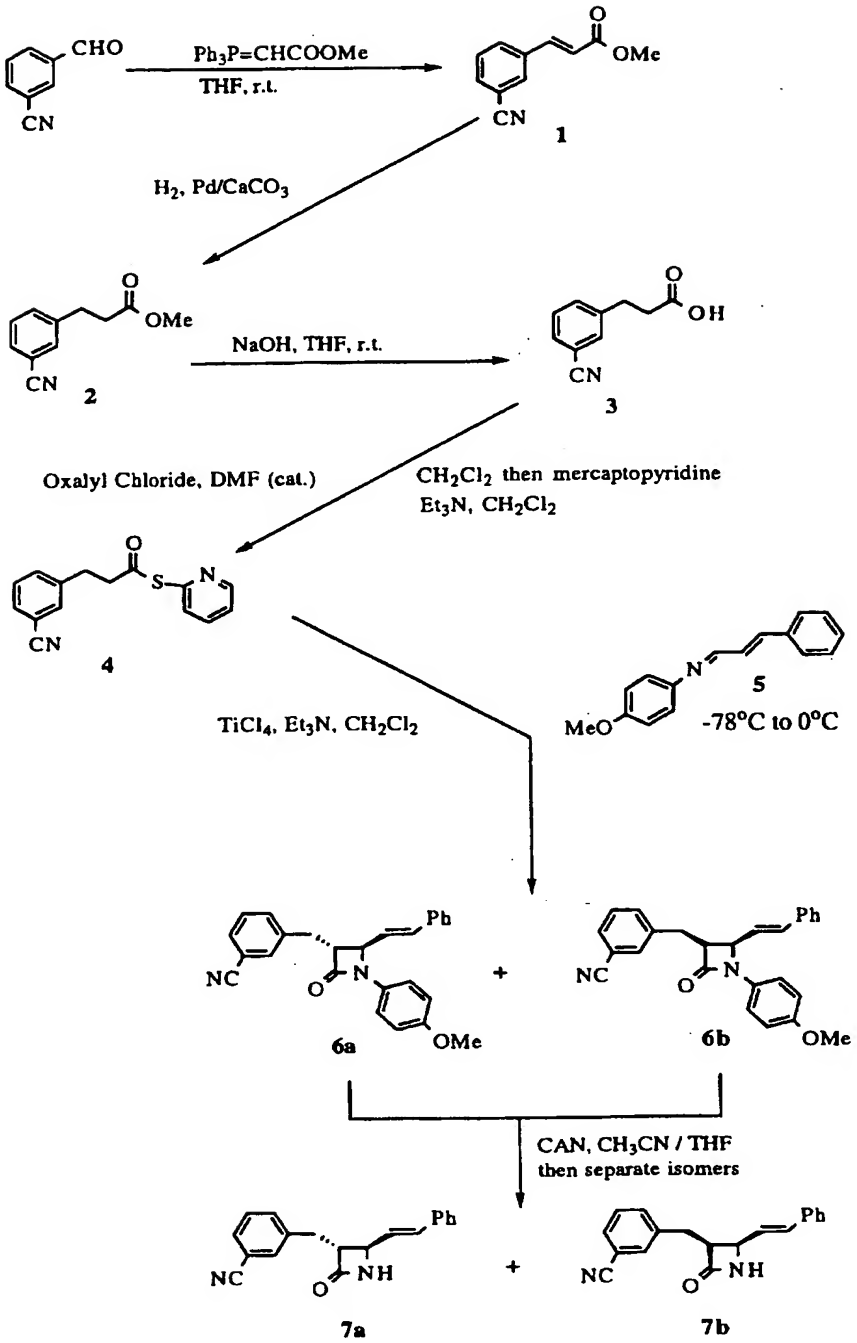


Compounds of Formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

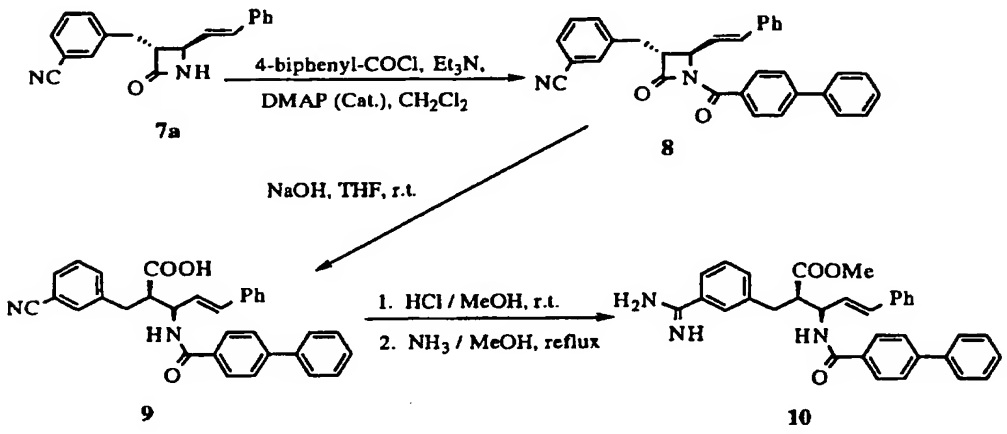
Scheme A exemplifies a general method for preparing intermediates for use in preparing compounds of formula I according to the invention.

SCHEME A


CHO
CN
Ph3P=CHCOOMe
THF, r.t.
O
OMe
CN
1
H2, Pd/CaCO3
O
OMe
CN
2
NaOH, THF, r.t.
O
OH
CN
3
Oxalyl Chloride, DMF (cat.)
CH2Cl2 then mercaptopyridine
Et3N, CH2Cl2
O
S
N
CN
4
TiCl4, Et3N, CH2Cl2
N
MeO
5
-78°C to 0°C
Ph
NC
O
N
OMe
6a
+
6b
CAN, CH3CN / THF
then separate isomers
NH
7a
7b

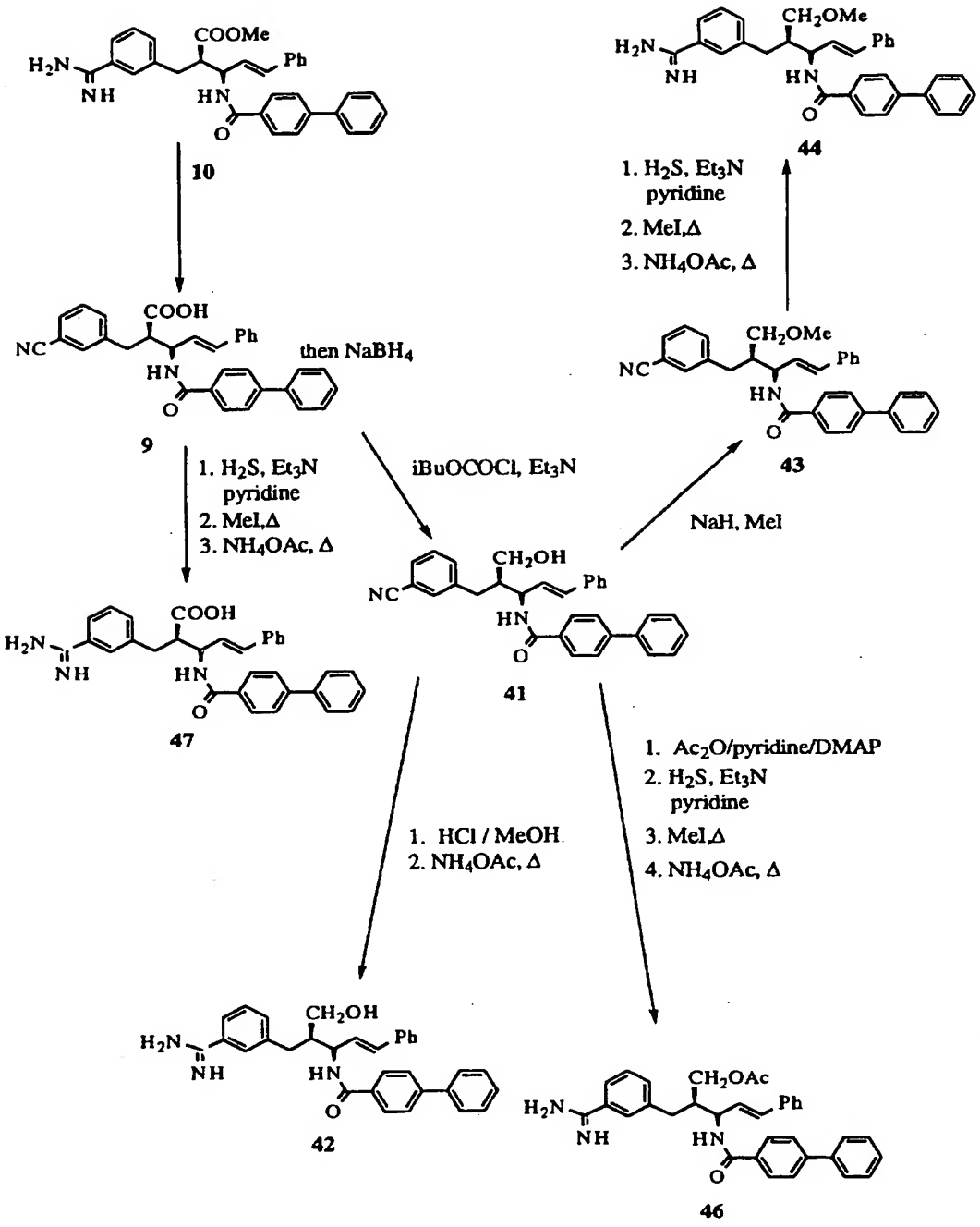
Scheme B exemplifies a general method for converting the intermediates prepared according to Scheme A to compounds of formula I according to the invention.

SCHEME B



Scheme C exemplifies a general method for effecting interconversions between compounds of formula I according to the invention.

SCHEME C

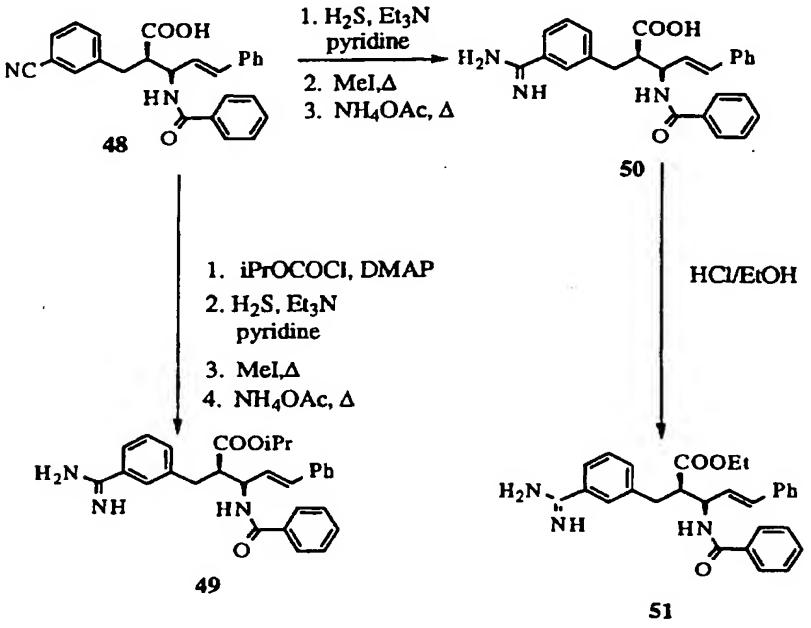


In addition, the compounds of formula 1 wherein R_3 is hydroxymethy may be converted to the corresponding thiolmethyl compounds by treating the alcohol

with an alkyl or aryl sulfonyl halide and displacing the alkyl or aryl sulfonate with NaSH. the thiolmethyl compounds may then be alkylated or acylated to give other compounds within the scope of the invention.

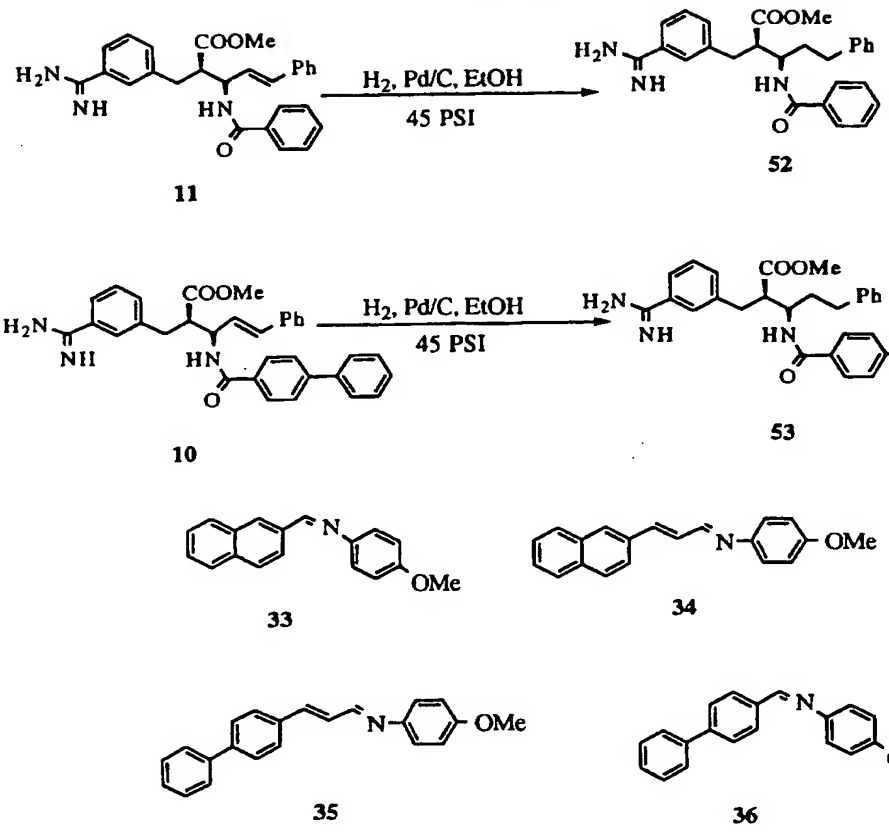
Scheme D exemplifies a general method for converting a nitrile intermediate to a compound of formula I and additional general methods for effecting interconversions between compounds of formula I according to the invention.

SCHEME D



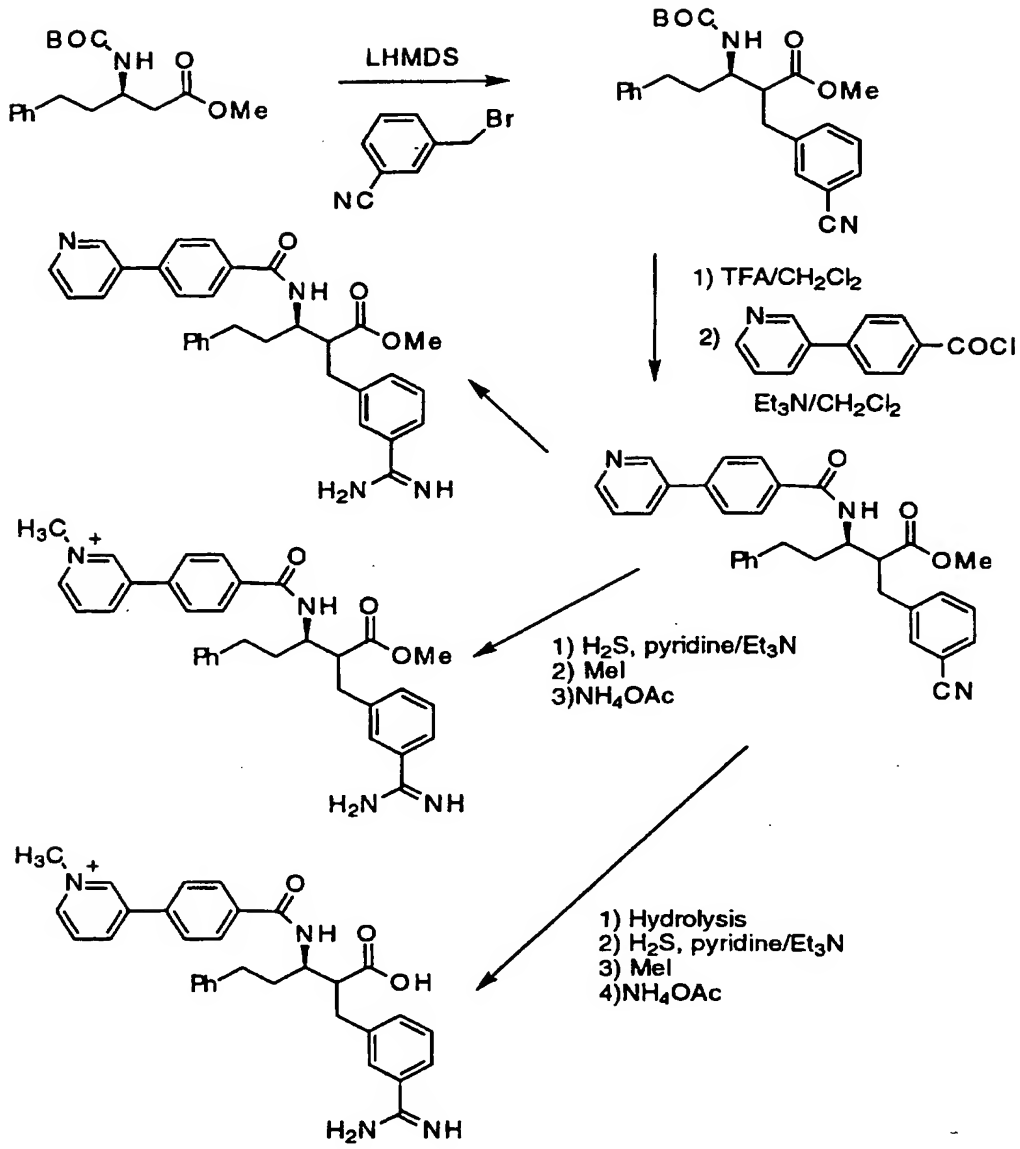
Scheme E exemplifies an additional general method for effecting interconversions between compounds of formula I according to the invention.

SCHEME E



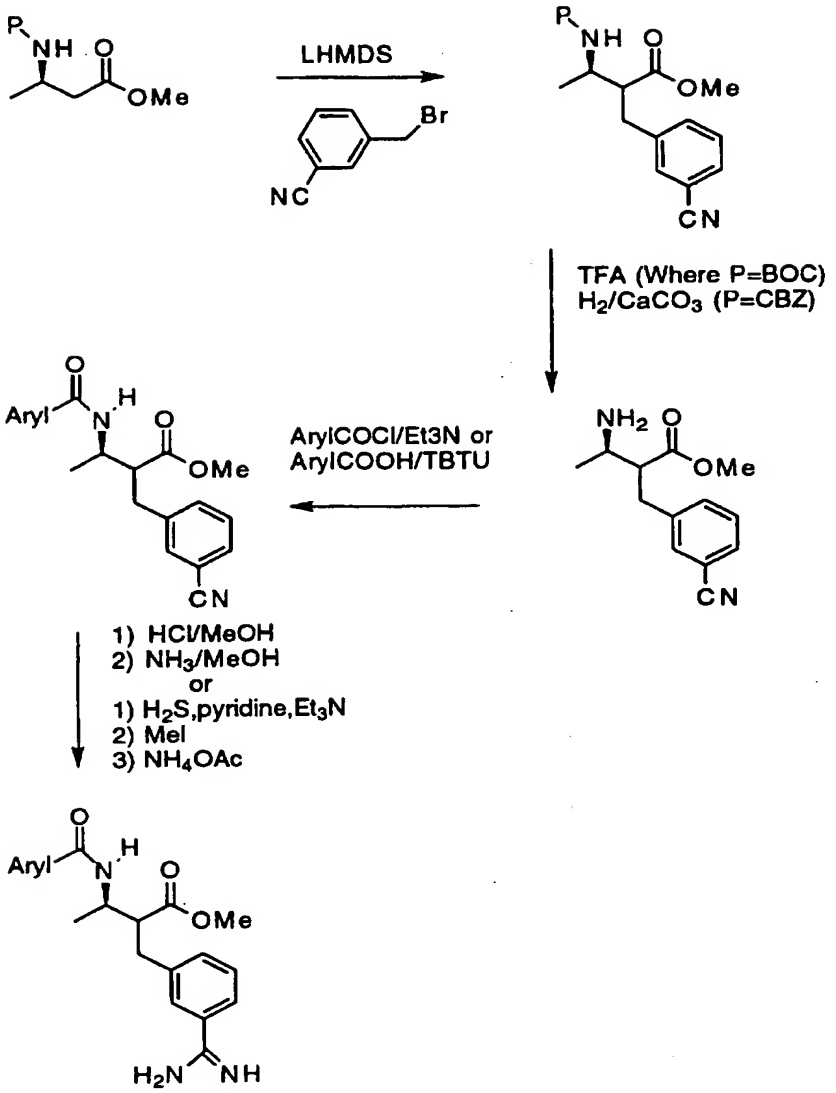
Scheme F exemplifies a general method for preparing compounds according to the present invention wherein R_4 of formula I is optionally substituted phenethyl.

Scheme F



Scheme G exemplifies a general method for preparing compounds according to the present invention wherein R_4 of formula I is methyl.

Scheme G



It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism, e.g., E or Z isomerism, and optical isomerism, e.g., R or S configurations. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. Individual geometrical isomers and stereoisomers within formula I, and their mixtures, are within the scope of the invention.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.
Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-B-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the

chosen metal in an aqueous or organic solvent with the free acid form of th compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

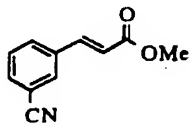
The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents, or by methods according to this invention.

The present invention is further exemplified but not limited by the following illustrative examples which illustrate the preparation of the compounds according to the invention.

In the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significance: s=singlet; d=doublet; t=triplet; m=multiplet; dd=doublet of doublets; ddd=doublet of doublets of doublets; dt=doublet of triplets, b=broad.

EXAMPLE 1

Compound **1**

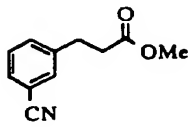


To a stirred solution of 3-cyanobenzaldehyde (20 g; 153 mmol) in 100 mL of dry THF under N_2 at room temperature is added methyl (triphenylphosphoranylidene)acetate (61.2 g; 183 mmol). The mixture is allowed to stir overnight at room temperature and then concentrated *in vacuo*. The crude residue is chromatographed (40% EtAc:Hexane) to give 27.3 g (96%) of the acrylate **1**.

^{1}H NMR ($CDCl_3$, d): 7.43 - 7.8 (m, 5H), 6.47 (d, J = 12 Hz, 1H), 3.8 (s, 3H).

EXAMPLE 2

Compound **2**



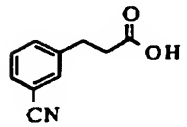
To a stirred solution of compound **1** (27.33 g) in 150 mL of EtOH is added 2 g of 10% Pd/$CaCO_3$. The resulting mixture is hydrogenated under 45 PSI H_2 on a

Parr shaker for 8 hours at room temperature. The mixture is then filtered through a plug of celite and the filtrate concentrated *in vacuo* to give 26.93 g (98 %) of **2** as a clear oil.

^{1}H NMR ($CDCl_3$, d): 7.33 - 7.72 (m, 4H), 3.66 (s, 3H), 2.97 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H).

EXAMPLE 3

Compound **3**

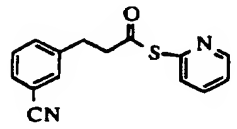


To a stirred solution of compound **2** (16.8 g; 89 mmol) in 200 mL of THF:MeOH (2:1) at room temperature is added 9 mL of 10 N NaOH solution dropwise. After 2h, most of the solvent is removed in vacuo and 30 mL of 5N HCl is added. The resulting mixture is extracted several times with EtAc. The combined extracts are dried ($MgSO_4$), filtered and concentrated to give 9.8 g (63%) of pure acid **3** as a white solid.

^{1}H NMR ($CDCl_3$, d): 7.35 - 7.55 (m, 4H), 2.98 (t, J = 7.9 Hz, 2H), 2.7 (t, J = 7.9 Hz, 2H).

EXAMPLE 4

Compound **4**



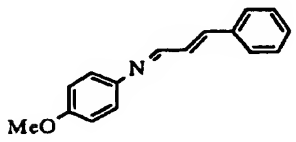
To a stirred solution of the carboxylic acid **3** (8.2 g; 47 mmol) an DMF (0.5 mL) in dry CH_2Cl_2 under N_2 at room temperature is added oxalyl chloride (6.1 mL;

70 mmol) dropwise. After 1 hour, gas evolution ceased and the solvent and excess oxalyl chloride is removed *in vacuo*. The residue is redissolved in 100 mL of dry CH_2Cl_2 and cooled to 0°C. Mercaptopyridine (5.6 g; 50 mmol) is added followed by triethylamine (7.9 mL; 56 mmol). The mixture is allowed to warm to r.t. and stirred for 1 hour. The mixture is diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer is dried (MgSO4), filtered and concentrated. The residue is chromatographed (eluent = 50% EtAc:Hexane) to give 5.12 g (84%) of the thioester **4** as a yellow oil.

^1H NMR ($CDCl_3$, d): 8.63 (d, J = 9 Hz, 1H), 7.7 - 7.8 (m, 1H), 7.27 - 7.62 (m, 6H), 3.05 (s, 4H).

EXAMPLE 5

Compound **5**

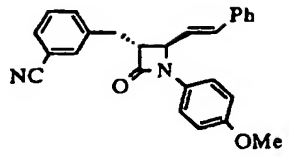


Added $MgSO_4$ (19.55 g; 162 mmol) to a stirred solution of cinnamaldehyde (10.2 mL; 81 mmol) and *p*-anisidine (10 g; 81 mmol) in 200 mL of CH_2Cl_2 under N_2 at 0°C. After 4 hours, the mixture is filtered and the filtrate concentrated to give 18.87 g (98 %) of the imine compound **5** as a gold: brown solid.

^1H NMR ($CDCl_3$, d): 8.28 (m, 1H), 7.52 (m, 2H), 7.38 (m, 3H), 7.2 (m, 2H), 7.12 (m, 2H), 6.93 (m, 2H), 3.82 (s, 3H).

EXAMPLE 6

Compound **6**



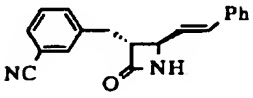
To a stirred solution of the thioester **5** (7 g; 26 mmol) in dry CH_2Cl_2 (120 mL) under N_2 at -78°C is added $TiCl_4$ solution (26.1 mL of 1 M solution in CH_2Cl_2). After 15 minutes, triethylamine (3.6 mL; 26 mmol) is added dropwise. The resulting mixture is allowed to stir for 1/2h at -78°C and then a solution of imine **1** (4.42 g ; 19 mmol in 20 mL CH_2Cl_2) is added dropwise. The mixture is then warmed to 0°C. After 1.5 hours at this temperature, the mixture is quenched with saturated $NaHCO_3$ solution and partitioned with water. The organic layer is washed with 1 N NaOH, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product is chromatographed (eluent = 40% EtAc:hexane) to give 2.42 g (32 %) of a 5:1 mixture of trans- /cis- b -lactam **6a** and **6b** as a gum.

Major trans-Isomer **6a**

^1H NMR ($CDCl_3$, d): 7.2 - 7.6 (m, 11H), 6.8 (d, J = 11 Hz, 2H), 6.65 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 4.32 (m, 1H), 3.72 (s, 3H), 3 - 3.42 (m, 3H).

EXAMPLE 7

Compound **7**



To a stirred solution of **6a, 6b** (1.5 g; 3.8 mmol) in 60 mL of THF/CH_3CN (1/3) at -20°C is added a solution of ceric ammonium nitrate (CAN, 3.13g; 5.7 mmol in
10 mL water). After 15 minutes, another 1.5 g of CAN in 5 mL of water is added. After a further 30 minutes, the mixture is quenched with saturated $NaHCO_3$

solution and allowed to come to room temperature. The resulting suspension is filtered through a bed of c lite, washing the celite pad s veral times with CH_2Cl_2 (total ca. 200 mL). The filtrate layers are separated and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product is chromatographed (eluent = 60% EtAc:hexane) to give 476 mg (43%) of pure *trans*-isomer **7a** together with 85 mg of a mixture of *cis*- **7b** and *trans* -**7a** isomers.

Major *trans* - isomer **7a**

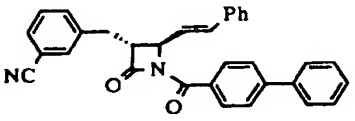
^1H NMR ($CDCl_3$, d): 7.17 - 7.65 (m, 9H), 6.52 (d, J = 15.8 Hz, 1H), 6.25 (s, 1H), 6.14 (dd, J = 15.8, 7.9 Hz, 1H), 3.97 (m, 1H), 3 - 3.33 (m, 3H).

Minor *cis* - isomer **7b**

^1H NMR ($CDCl_3$, d): 7.21 - 7.52 (m, 9H), 6.62 (d, J = 15.8 Hz, 1H), 6.45 (s, 1H), 6.1 (dd, J = 15.8, 7.9 Hz, 1H), 4.46 (m, 1H), 3.7 (m, 1H), 3.02 - 3.17 (m, 1H), 2.8 - 2.93 (m, 1H).

EXAMPLE 8

Compound **8**

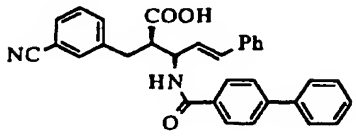


To a stirred solution of the trans-b-lactam **7a** in dry CH_2Cl_2 under N_2 at r.t. is added triethylamine (4.04 mL; 29 mmol) dropwise. Biphenylcarbonyl chloride (5.05g; 23.2 mmol) is then added followed by DMAP (50 mg). After 30 minutes the mixture is diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is then dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 30% EtAc:Hexane) gave 2.19 g (81 %) of the product **8** as a solid.

^{1}H NMR ($CDCl_3$, d): 8.06 (m, 2H), 7.2 - 7.75 (m, 16H), 6.67 (d, J = 15.8, Hz, 1H), 6.23 (dd, J = 15.8, 7.9 Hz, 1H), 4.63 (m, 1H), 3.46 (m, 1H), 3.1 - 3.3 (m, 2H).

EXAMPLE 9

Compound **9**

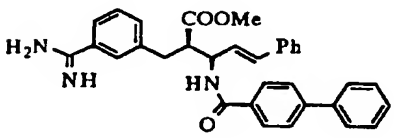


To a stirred solution of the b-lactam **8** (2.19 g; 4.7 mmol) in 50 mL of THF at r.t. is added 1 N NaOH solution (13.6 mL) dropwise. After 2 hours, most of the THF is removed *in vacuo* and 20 mL of 1 N HCl is added. The resulting mixture is extracted with EtAc. The extract is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product is purified by RPHPLC (CH_3CN:water, 0.1% TFA, 40 - 100 gradient) and the fractions containing product are lyophilized to give 1.1 g (50%) of carboxylic acid **9** as a white solid.

^{1}H NMR ($CDCl_3$, d): 7.18 - 7.97 (m, 18H), 6.61 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 5.14 (m, 1H), 3 - 3.22 (m, 3H).

EXAMPLE 10

Compound **10**



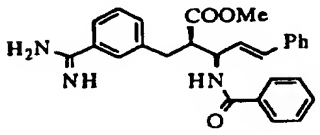
To a stirred solution of the carboxylic acid **9** (105 mg; 0.22 mmol) in 3 mL of dry MeOH at r.t. is added molecular sieves (ca. 50 mg). Gaseous HCl is then bubbled in for ca. 2 minutes. The mixture is then allowed to stir over night at room temperature and then concentrated under a stream of N_2. A solution of

NH_3 in MeOH (3 mL of 7 N solution) is then added to the r sidue and the mixture refluxed for 1.5 hours, allowed to cool and the solvent removed *in vacuo*. The residue is purified by RPHPLC (CH_3CN: water: 0.1% TFA, 40-100 gradient) and the fractions containing product are lyophilized to give 73 mg (53 %) of the product **10** as a white solid.

^1H NMR (DMSO-d_6, d): 8.7 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.75 - 7.21 (m, 14H), 6.67 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.8 Hz, 1H), 4.98 (dd, J = 16.1, 7.8 Hz, 1H), 3.46 (s, 3H), 3.25 - 3.18 (m, 1H), 3.05 - 2.88 (m, 2H).

EXAMPLE 11

Compound **11**

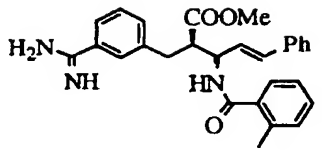


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **11** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (MeOH-d_4, d): 8.61 (d, J = 11.3 Hz, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.15 - 7.67 (m, 14H), 6.67 (d, J = 15.8 Hz, 1H), 6.3 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 3.55 (s, 3H), 3.27 (m, 1H), 3.1 (m, 2H).

EXAMPLE 12

Compound **12**

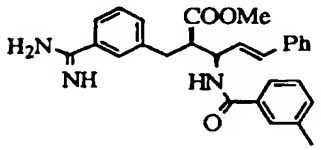


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** *o*-Toluoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **12** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.3 (s, 1H), 9.15 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.7 (d, J = 8 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.2 - 7.6 (m, 12H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 15, 6 Hz, 1H), 3.55 (s, 3H), 3.2 - 3.3 (m, 1H), 2.8 - 3 (m, 1H), 2.3 (s, 3H).

EXAMPLE 13

Compound **13**

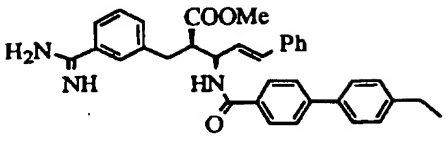


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** *m*-Toluoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **13** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.3 (s, 1H), 9.2 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.7 (d, J = 8 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.2 - 7.6 (m, 12H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 16, 6 Hz, 1H), 3.6 (s, 3H), 3.2 - 3.3 (m, 1H), 2.8 - 3 (m, 1H), 2.35 (s, 3H).

EXAMPLE 14

Compound **14**

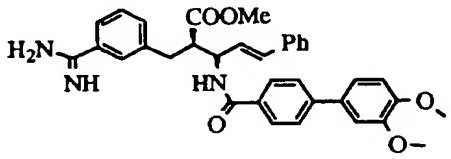


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **14** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.3 (s, 1H), 9.15 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.2 (d, J = 8 Hz, 2H), 8 (d, J = 9 Hz, 2H), 7.4 - 7.9 (m, 12H), 7.2 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.1 - 3.2 (m, 1H), 2.85 (q, 2H), 1.4 (t, 3H).

EXAMPLE 15

Compound **15**

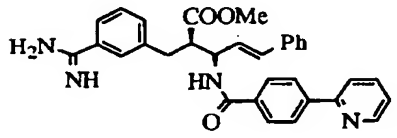


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 3', 4' - Dimethoxy - 4 - biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **15** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^{1}H NMR (DMSO-d_6, d): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.1 (d, J = 8 Hz, 2H), 7.9 (d, J = 9 Hz, 2H), 7.8 (s, 2H), 7.4 - 7.7 (m, 11H), 7.25 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.4 (dd, J = 15, 6 Hz, 1H), 4 (s, 3H), 3.9 (s, 3H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 16

Compound **16**

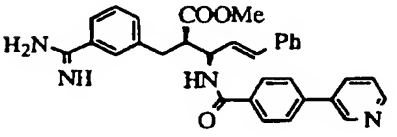


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4-(2'-pyridyl)benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **16** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^{1}H NMR (DMSO-d_6, d): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.8 (s, 1H), 8.4 (d, J = 8 Hz, 2H), 8.3 (d, J = 9 Hz, 1H), 8.1 (d, J = 8 Hz, 2H), 7.9 (s, 2H), 7.4 - 7.8 (m, 10H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 17

Compound **17**



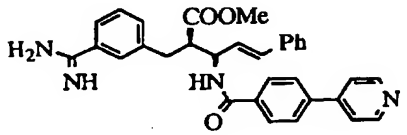
This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4-(3'-Pyridyl)benzoyl chloride is

substituted for 4-biphenylcarbonyl chlorid in the b-lactam acylation step. The final product **17** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.5 (s, 1H), 8.2 (d, J = 8 Hz, 2H), 8.1 (d, J = 9 Hz, 2H), 8 (d, J = 8 Hz, 1H), 7.9 (s, 2H), 7.4 - 7.8 (m, 9H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 18

Compound **18**

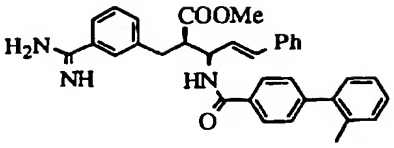


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4-(4'-Pyridyl)benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **18** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.5 (s, 1H), 9.3 (s, 1H), 9 (d, J = 7.6 Hz, 1H), 8.2 (s, 4H), 7.8 (s, 2H), 7.5 - 7.8 (m, 11H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 19

Compound **19**

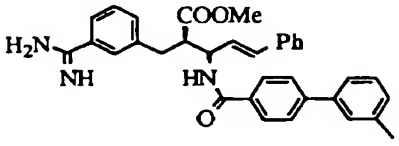


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 2'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **19** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 1H), 9.03 (s, 1H), 8.71 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 7.6 - 7.12 (m, 13H), 6.67 (d, J = 15.9 Hz, 1H), 6.42 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.32 (s, 3H), 3.3 - 3.15 (m, 1H), 3.11 - 2.9 (m, 2H), 2.21 (s, 3H).

EXAMPLE 20

Compound **20**

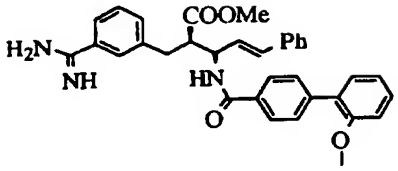


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 3'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **20** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 1H), 8.99 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.68 - 7.15 (m, 13H), 6.68 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 3.1 - 2.9 (m, 2H), 2.36 (s, 3H).

EXAMPLE 21

Compound **21**

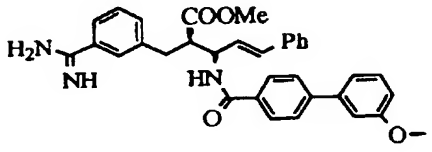


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4** 2'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **21** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 1H), 9.03 (s, 1H), 8.76 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 9.5 Hz, 2H), 7.65 - 6.95 (m, 15H), 6.64 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.75 (s, 3H), 3.46 (s, 3H), 3.3 - 3.17 (m, 1H), 3.1 - 2.9 (m, 2H).

EXAMPLE 22

Compound **22**

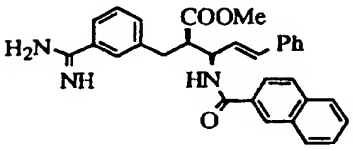


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4** 3'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **22** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^{1}H NMR (DMSO-d_6, d): 9.23 (s, 1H), 8.96 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9.6 Hz, 2H), 7.68 - 7.18 (m, 12H), 6.96 (dd, J = 9.6, 2 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.9 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.28 - 3.17 (m, 1H), 3.08 - 2.86 (m, 2H).

EXAMPLE 23

Compound **23**

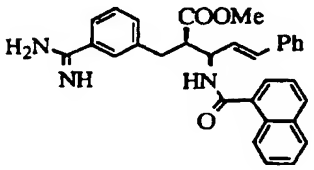


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 2-Naphthylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **23** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^{1}H NMR (DMSO-d_6, d): 9.24 (s, 1H), 9.02 (s, 1H), 8.83 (d, J = 8.6 Hz, 1H), 8.4 (s, 1H), 8.08 - 7.85 (m, 4H), 7.68 - 7.2 (m, 12H), 6.68 (d, J = 15.8 Hz, 1H), 6.43 (dd, J = 15.8, 7.8 Hz, 1H), 5.03 (dd, J = 15.8, 7.8 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.2 (m, 1H), 3.13 - 2.95 (m, 2H).

EXAMPLE 24

Compound **24**

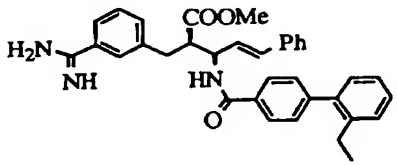


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 1-Naphthylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **24** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.27 (s, 1H), 9.11 (s, 1H), 8.88 (d, J = 8.67 Hz, 1H), 8.18 - 8.07 (m, 1H), 8.05 - 7.9 (m, 2H), 7.7 - 7.2 (m, 13H), 6.73 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.07 (dd, J = 16, 7.9 Hz, 1H), 3.52 (s, 3H), 3.28 - 3.17 (m, 1H), 3.12 - 2.95 (m, 2H).

EXAMPLE 25

Compound **25**

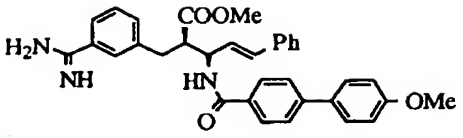


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 3'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **25** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 1H), 9.05 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.62 (m, 2H), 7.55 - 7.15 (m, 11H), 6.66 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 4.96 (dd, J = 16, 7.8 Hz, 1H), 3.47 (s, 3H), 3.3 - 3.18 (m, 1H), 3.1 - 2.88 (m, 2H), 2.67 (q, J = 8.5 Hz, 2H), 1.22 (t, J = 8.5 Hz, 3H).

EXAMPLE 26

Compound **26**

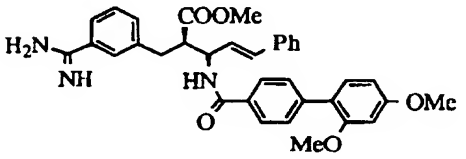


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **26** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.23 (s, 1H), 8.96 (s, 1H), 8.66 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9.1 Hz, 2H), 7.72 - 7.22 (m, 11H), 7.03 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.9 Hz, 1H), 4.97 (dd, J = 16.1, 7.9 Hz, 1H), 3.77 (s, 3H), 3.46 (s, 3H), 3.28 - 3.15 (m, 1H), 3.08 - 2.88 (m, 2H).

EXAMPLE 27

Compound **27**



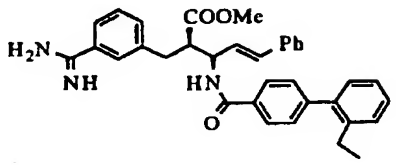
This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 2', 4'- Dimethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **27** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.23 (s, 1H), 9.07 (s, 1H), 8.63 (d, J = 9 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.68 - 7.15 (m, 14H), 6.72 - 6.52 (m, 1H), 6.45 - 6.3 (m, 1H),

5.04 - 4.9 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 3.21 - 3.15 (m, 1H), 3.08 - 2.85 (m, 2H).

EXAMPLE 28

Compound **28**

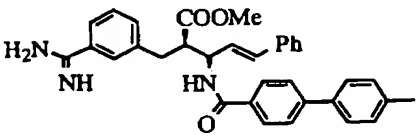


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 2'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **28** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 1H), 8.92 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 9 Hz, 2H), 7.68 - 7.08 (m, 15H), 6.65 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 2.52 (q, J = 9.6 Hz, 2H), 0.98 (t, J = 9.6 Hz, 3H).

EXAMPLE 29

Compound **29**



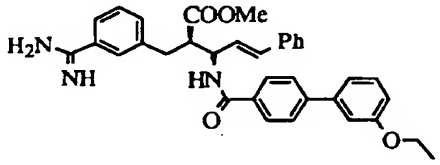
This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The

final product **29** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.22 (s, 1H), 8.91 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.65 - 7.2 (m, 13H), 6.65 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 3.08 - 2.88 (m, 2H), 2.35 (s, 3H).

EXAMPLE 30

Compound **30**

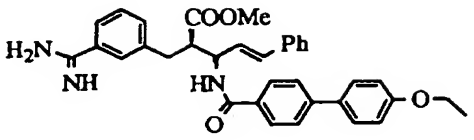


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 3'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **30** is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.22 (s, 1H), 9.05 (s, 1H), 8.7 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.68 - 7.12 (m, 12H), 6.98 - 6.85 (m, 1H), 6.67 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 5.01 (dd, J = 16, 7.8 Hz, 1H), 4.08 (q, J = 7.5 Hz, 2H), 3.45 (s, 3H), 3.25 - 3.15 (m, 1H), 3.08 - 2.89 (m, 2H), 1.32 (t, J = 7.5 Hz, 2H).

EXAMPLE 31

Compound **31**

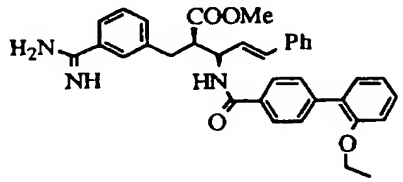


This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 4'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **31** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.26 (s, 1H), 9.02 (s, 1H), 8.64 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 9 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 7.7 - 7.22 (m, 11H), 7.01 (d, J = 10.4 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.06 (q, J = 8.2 Hz, 2H), 3.45 (s, 3H), 3.3 - 3.18 (m, 1H), 3.08 - 2.85 (m, 2H), 1.32 (t, J = 8.2 Hz, 3H).

EXAMPLE 32

Compound **32**



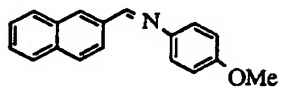
This compound is prepared in a manner similar to compound **10** above starting from imine **5** and thioester **4.** 2'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **32** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.24 (s, 1H), 9.11 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.59 - 6.95 (m, 13H), 6.65 (d, J = 15.9 Hz,

1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.03 (q, J = 8.1 Hz, 2H), 3.47 (s, 3H), 3.28 - 3.18 (m, 1H), 3.1 - 2.88 (m, 2H), 1.24 (t, J = 8.1 Hz, 3H).

EXAMPLE 33

Compound **33**

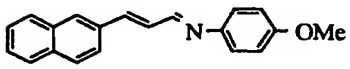


To a stirred solution of 2-Naphthaldehyde (20 g; 0.13 mol) in 200 mL of CH_2Cl_2 at room temp. is added p-anisidine (15.8 g; 0.13 mol) followed by anhydrous magnesium sulfate (16.9 g; 0.14 mol). After 3.5 hours, the mixture is filtered and the filtrate concentrated *in vacuo* to give 31.5 g (92%) of the imine **33.**

^{1}H NMR ($CDCl_3$, d): 8.64 (s, 1H), 8.19 (m, 2H), 7.78 - 7.98 (m, 3H), 7.43 - 7.56 (m, 2H), 7.32 (m, 2H), 6.96 (m, 2H), 3.83 (s, 3H).

EXAMPLE 34

Compound **34**

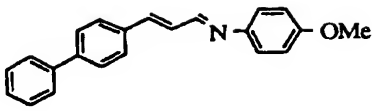


Prepared using *trans* - 3- (2'-naphthyl)acrolein, p-anisidine and anhydrous magnesium sulfate as described for compound **33** above.

^{1}H NMR ($CDCl_3$, d): 8.35 (d, J = 9 Hz, 1H), 7.78 - 7.9 (m, 4H), 7.72 (m, 1H), 7.5 (m, 2H), 7.25 (m, 4H), 6.93 (m, 2H), 3.82 (s, 3H).

EXAMPLE 35

Compound **35**

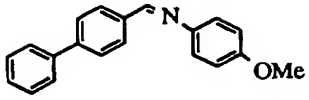


Prepared using *trans*- 3 - (4'-biphenyl)acrolein, p-anisidine and anhydrous magnesium sulfate as described for compound **33** above.

^{1}H NMR ($CDCl_3$, d): 8.33 (d, J = 9 Hz, 1H), 7.2 - 7.68 (m, 13H), 6.9 (m, 2H), 3.82 (s, 3H).

EXAMPLE 36

Compound **36**

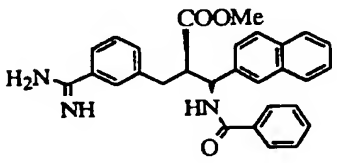


Prepared using 4-biphenylcarboxaldehyde, p-anisidine and anhydrous magnesium sulfate as described for compound **33** above.

^{1}H NMR ($CDCl_3$, d): 8.52 (s, 1H), 7.97 (m, 2H), 7.62 - 7.73 (m, 4H), 7.35 - 7.52 (m, 3H), 7.27 (m, 2H), 6.95 (m, 2H), 3.85 (s, 3H).

EXAMPLE 37

Compound **37**



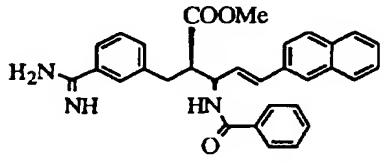
This compound is prepared in a manner similar to compound **10** starting from imine **33** and thioester **4.** Benzoyl chloride is substituted for 4-

biphenylcarbonyl chloride in the b-lactam acylation step. The final product **37** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (MeOH-d_4, d): 9.01 (d, J = 9.4 Hz, 1H), 7.77 - 7.98 (m, 6H), 7.43 - 7.67 (m, 9H), 5.53 (m, 1H), 3.56 (m, 1H), 3.54 (s, 3H), 3.1 (m, 1H), 2.81 (m, 1H).

EXAMPLE 38

Compound **38**

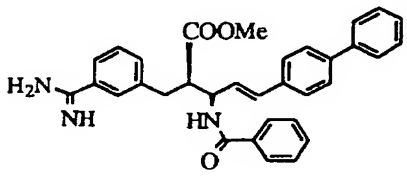


This compound is prepared in a manner similar to compound **10** starting from imine **34** and thioester **4.** Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **38** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.27 (s, 2H), 9.1 (s, 2H), 8.72 (d, 1H), 7.4 - 7.95 (m, 16H), 6.86 (d, J = 18 Hz, 1H), 6.54 (dd, J = 10, 6 Hz, 1H), 5.03 (m, 1H), 3.48 (s, 3H), 3.32 (m, 1H), 3.04 (m, 2H).

EXAMPLE 39

Compound **39**



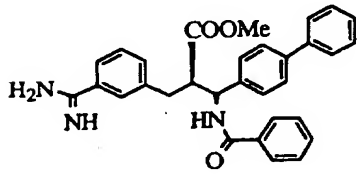
This compound is prepared in a manner similar to compound **10** starting from imine **35** and thioester **4.** Benzoyl chloride is substituted for 4-

biphenylcarbonyl chloride in the b-lactam acylation step. The final product **39** is purifi_d by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.25 (s, 2H), 9.11 (s, 2H), 8,74 (d, 1H), 7.30 - 8 (m, 22H), 6.23 (d, J = 18 Hz, 1H), 6.47 (dd, J = 18, 6 Hz, 1H), 5.04 (m, 1H), 3.49 (s, 3H), 3.3 (m, 1H), 3.03 (m, 2H).

EXAMPLE 40

Compound **40**

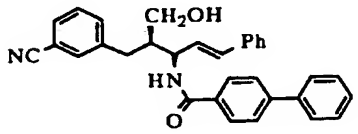


This compound is prepared in a manner similar to compound **10** starting from imine **36** and thioester **4**. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product **40** is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized.

^1H NMR (DMSO-d_6, d): 9.23 (s, 2H), 9.05 (s, 2H), 8.97 (s, 2H), 7.28 - 7.8 (m, 18H), 5.35 (t, 1H), 3.42 (s, 3H), 3.31 (m, 1H), 2.89 (dd, 1H), 2.6 (dd, 1H).

EXAMPLE 41

Compound **41**



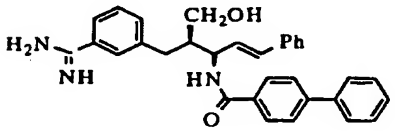
To a stirring solution of the carboxylic acid **9** (980 mg; 2 mmol) and triethylamine (0.44 mL; 3.2 mmol) in dry THF under N_2 at 0°C is added i-butylchloroformate (0.39 mL; 3 mmol) dropwise. After 15 minut s, a solution of

sodium borohydride (153 mg; 4 mmol in 5 mL water) is added dropwise. The mixture is allowed to warm up to room temperature. After 1 hour, most of the THF is removed *in vacuo*. Water is then added and the mixture extracted with ethyl acetate. The combined extracts are dried ($MgSO_4$), filtered and concentrated. The crude product is purified by chromatography (eluent = 35% EtAc:Hexane) to give 720 mg (76%) of the alcohol 41.

^1H NMR ($CDCl_3$, d): 7.92 (d, J = 9 Hz, 2H), 7.2 - 7.72 (m, 16H), 6.67 (d, J = 15.5 Hz, 1H), 6.27 (dd, J = 15.5, 7.8 Hz, 1H), 4.94 (m, 1H), 3.88 (m, 1H), 3.5 (m, 1H), 3.12 (m, 1H), 2.82 - 3.03 (m, 2H), 1.95 (m, 1H).

EXAMPLE 42

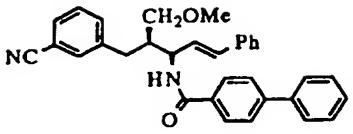
Compound **42**



To a stirred solution of the alcohol **41** (106 mg; 0.22 mmol) in 3 mL of dry MeOH at r.t. is added molecular sieves (ca. 50 mg). Gaseous HCl is then bubbled in for ca. 2 minutes The mixture is then allowed to stir over night at room temperature and then concentrated under a stream of N_2. A solution of NH_3 in MeOH (3 mL of 7 N solution) is then added to the residue and the mixture refluxed for 1.5 hour, allowed to cool and the solvent removed *in vacuo*. The residue is purified by RPHPLC (CH_3CN: water: 0.1% TFA, 40-100 gradient) and the fractions containing product are lyophilized to give 29 mg (22 %) of the product **42** as the trifluoroacetate salt.

EXAMPLE 43

Compound **43**

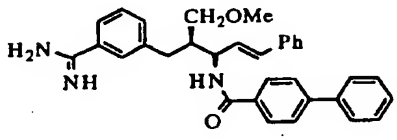


To a stirring solution of the alcohol compound (88 mg; 0.2 mmol) in 2 mL of 2:1 THF:DMF under N_2 at 0°C is added NaH (15 mg of 60% dispersion; 0.4 mmol). After 15 minutes, methyl iodide (0.02 mL; 0.3 mmol) is added and the mixture allowed to warm to room temperature. After 2 hours, the mixture is quenched with saturated $NaHCO_3$ solution. Most of the THF is removed *in vacuo* and the residue diluted with water and extracted with CH_2Cl_2. The combined extracts are dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 35% EtAc:Hexane) to give 21 mg (23%) of the product **43** together with 34 mg of recovered alcohol **41**.

^1H NMR ($CDCl_3$, d): 7.93 (d, J = 9.3 Hz, 2H), 7.15 - 7.83 (m, 16H), 6.57 (d, J = 15.8 Hz, 1H), 6.22 (dd, J = 15.8, 6.8 Hz, 1H), 5 (m, 1H), 3.75 (m, 1H), 3.42 (s, 3H), 3.27 (m, 1H), 2.87 - 3.03 (m, 2H), 2.12 (m, 1H).

EXAMPLE 44

Compound **44**



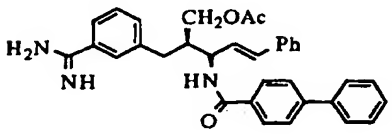
Into a stirring solution of compound **43** (20 mg; 0.04 mmol) in 1.5 mL of 2:1 pyridine:Et_3N is bubbled H_2S for about 1 minute. The mixture is allowed to stir overnight at room temperature and then concentrated under a stream of N_2 and then taken up into 2 mL of CH_2Cl_2. Methyl iodide (1 mL) is added and the mixture refluxed for 1 hour. The solvent is then removed *in vacuo*, the residue taken up into 2 mL of MeOH and NH_4OAc (30 mg) is added. The resulting mixture is refluxed for 1 hour and then allowed to cool. The solvent is then

removed *in vacuo* and the residue is purified by RPHPLC (CH_3CN:H_2O, 0.1% TFA, 40 to 100% CH_3CN gradient) and the fractions containing product are lyophilized to give 13 mg (51%) of product **44** as the trifluoroacetate salt.

^1H NMR (MeOH-d_4, d): 8.47 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 2H), 7.17 - 7.73 (m, 14 H), 6.55 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.8, 7.9 Hz, 1H), 4.77 (m, 1H), 3.7 (dd, J = 9.5, 3.1 Hz, 1H), 3.47 (dd, J = 9.5, 3.1 Hz, 1H), 3 (d, J = 7.9 Hz, 2H), 2.35 (m, 1H).

EXAMPLE 45

Compound **45**

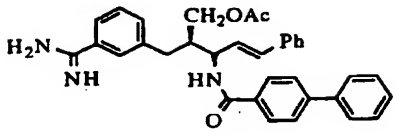


A mixture of alcohol **41** (480 mg; 1 mmol), pyridine (0.40 mL; 4.9 mmol) and acetic anhydride (0.12 mL; 1.2 mmol) is stirred overnight at room temperature. The next day, 3 drops of pyridine and acetic anhydride are added. The next day, the reaction is not complete and so 4 mg of DMAP is added. After 1 hour, the reaction is complete by tlc. The mixture is diluted with CH_2Cl_2 and washed with 0.1 N HCl solution. The organic layer is dried ($MgSO_4$), filtered and concentrated to give 520 mg of **45**.

^1H NMR ($CDCl_3$, d): 7.98 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.17 - 7.58 (m, 12H), 6.94 (d, 1H), 6.55 (d, J = 18 Hz, 1H), 6.21 (dd, J = 18, 5 Hz, 1H), 5.1 (m, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 2.68 - 2.97 (m, 2H), 2.51 (m, 1H).

EXAMPLE 46

Compound **46**

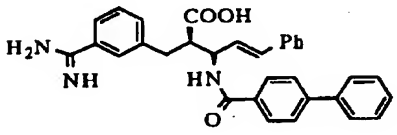


Compound **45** is converted to the corresponding amidine **46** using the hydrogen sulfide /methyl iodide: ammonium acetate sequence described for the conversion of **43** to **44**. The product **46** is purified by RPHPLC and isolated as its trifluoroacetate salt.

^{1}H NMR (DMSO-d_6, d): 9.31 (s, 2H), 8.97 (s, 2H), 8.7 (d, 1H), 7.18 - 8 (m, 18H), 6.6 (d, J = 18 Hz, 1H), 6.40 (dd, J = 18, 6 Hz, 1H), 4.83 (m, 1H), 4.02 (m, 1H), 3.84 (m, 2H), 2.95 (m, 1H), 2.57 (m, 1H), 1.93 (s, 3H).

EXAMPLE 47

Compound **47**

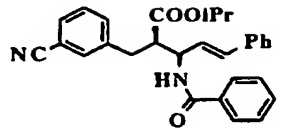


Carboxylic acid **9** is converted to its corresponding amidine **47** using the hydrogen sulfide: methyl iodide: ammonium acetate sequence described for the conversion of **43** to **44**. The product **47** is isolated by RPHPLC as its trifluoroacetate salt.

^{1}H NMR (MeOH-d_4, d): 8 (d, J = 9 Hz, 2H), 7.82 (d, J = 9 Hz, 2H), 7.22 - 7.77 (m, 14H), 6.73 (d, J = 15.8 Hz, 1H), 6.4 (dd, J = 15.8, 7.9 Hz, 1H), 4.95 (m, 1H), 3.08 - 3.45 (m, 3H).

EXAMPLE 49

Compound **49**

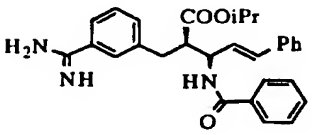


To a stirring solution of the carboxylic acid **48** (120 mg; 0.29 mmol) in 5 mL of dry CH_2Cl_2 under N_2 at room temperature is added triethylamine (0.05 mL; 0.38 mmol). iso-propyl chloroformate (0.38 mL of 1 M solution in toluene) is added dropwise. After 30 minutes, DMAP (18 mg; 0.15 mmol) is added and the mixture allowed to further stir for 1.5 hours at room temperature. The mixture is then diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is then dried ($MgSO_4$), filtered and concentrated. The crude product is chromatographed (eluent = 40% EtAc:Hexane to give 44 mg (33 %) of the corresponding isopropyl ester. This compound is then converted to the corresponding amidine **49** via the hydrogen sulfide: methyl iodide: ammonium acetate procedure as described for the conversion of **43** to **44**. The product **49** is purified by RPHPLC and isolated as its trifluoroacetate salt.

^{1}H NMR (MeOH-d_4, d): 8.6 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.16 - 7.7 (m, 12H), 6.69 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 4.85 (m, 1H), 3.23 (m, 1H), 3.08 (m, 2H), 1.07 (d, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H).

EXAMPLE 50

Compound **50**

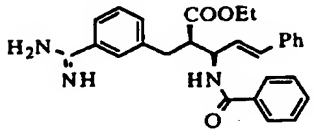


This compound is prepared by conversion of **48** to the corresponding amidine using the hydrogen sulfide: methyl iodide: ammonium acetate sequence described for the conversion of **43** to **44**. The product **50** is purified by RPHPLC and isolated as its trifluoroacetate salt.

^{1}H NMR (MeOH-d_4, d): 8.6 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.16 - 7.7 (m, 12H), 6.69 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 4.85 (m, 1H), 3.23 (m, 1H), 3.08 (m, 2H), 1.07 (d, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H).

EXAMPLE 51

Compound **51**

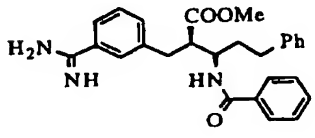


Into a stirred solution of the carboxylic acid **50** (96 mg; 0.18 mmol) in 3 mL of EtOH at room temperature is bubbled HCl for ca. 3 minutes. The mixture is allowed to stir for 7 hours at room temperature and then stored in the refrigerator (0°C) over the weekend. The solvent is then removed *in vacuo* and the residue purified by RPHPLC. The product **51** is isolated as its trifluoroacetate salt.

^{1}H NMR (MeOH-d_4, d): 8.63 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8 Hz, 2H), 7.16 - 7.68 (m, 12H), 6.68 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 5 (m, 1H), 4.02 (q, 2H), 3.25 (m, 1H), 3.07 (d, J = 7.9 Hz, 2H), 1.05 (t, 3H).

EXAMPLE 52

Compound **52**



A mixture of compound and 10% Pd/C (25 mg) in EtAc (2 mL): EtOH (5 mL) is hydrogenated und r 45 PSI H_2 for 19 hours at room temperature. The mixture

is then filtered through a bed of celite and the filtrate concentrated. The crude product is purified by RPHPLC (CH_3CN:water: 0.1 % TFA, 10 - 100% CH_3CN gradient) and the fractions containing product are lyophilized to give 21 mg of **52**.

^1H NMR (MeOH-d_4, d): 8.27 (d, J = 9.3 Hz, 1H), 7.83 (m, 2H), 7.43 - 7.65 (m, 7H), 7.09 - 7.27 (m, 5H), 4.35 (m, 1H), 3.58 (s, 3H), 2.95 - 3.15 (m, 3H), 2.54 - 2.75 (m, 2H), 1.93 (m, 2H).

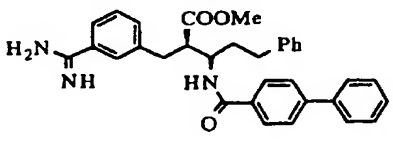
Resolution of Compound **10**

Racemic compound **10** (ca. 650 mg, single diastereomer with the presumed syn-stereochemistry shown) is resolved into its two enantiomers **53** (late eluting isomer) and **54** (early eluting isomer) using preparative HPLC (Chiralpak AD column, 50 mm ID x 500 mm, 15 microns). The mobile phase is heptane (A) with 0.1% TFA and i-propanol (B) with 0.1% TFA, isocratic 20% A, 80% B (Flow = 200 mL: minute). The late eluting isomer is isolated by concentration *in vacuo*. The yield is 180 mg. The %ee enantiomer **53** is found to be 100% by analytical HPLC (Chiralpak AD). The ^1H NMR spectra for **53** and **54** are identical.

^1H NMR (DMSO-d_6, d): 8.7 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.75 - 7.21 (m, 14H), 6.67 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.8 Hz, 1H), 4.98 (dd, J = 16.1, 7.8 Hz, 1H), 3.46 (s, 3H), 3.25 - 3.18 (m, 1H), 3.05 - 2.88 (m, 2H).

EXAMPLE 55

Compound **55**

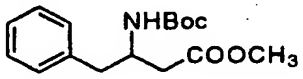


The hydrogenation of compound **53** (late luting enantiomer) is carri d out as for compound **52** above except ethyl acetate is omitted. The product is purified by RPHPLC (CH_3CN:water: 0.1 % TFA, 40 - 100% CH_3CN) and the product **55** is isolated as the trifluoroacetate salt.

^1H NMR (MeOH-d_4, d): 8.3 (d, J = 9.3 Hz, 1H), 7.84 (m, 2H), 7.07 - 7.8 (m, 16H), 4.37 (m, 1H), 3.6 (s, 3H), 2.97 - 3.17 (m, 3H), 2.57 - 2.77 (m, 2H), 1.95 (m, 2H).

EXAMPLE 56

Compound **56**

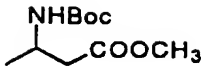


To a solution of N-α-Boc-D-Phenylalanine (38 mmol) in 80 mL of dry tetrahydrofuran is added N-methyl morpholine (38 mmol) in a single portion, followed by isobutyl chloroformate (38 mmol) in a similar fashion, at -20°C. The reaction mixture is stirrec for 10 minutes at -20°C and filtered into a preformed ethereal solution of diazomethane (~70 mmol) at 0°C. The resulting solution is allowed to stand at 0°C for 20 minutes. Excess diazomethane is decomposed by the dropwise addition of glacial acetic acid and solvents are removed *in vacuo*.

The resulting oil is dissolved in 150 mL of dry methanol. A solution of silver benzoate (8 mmol) in 17 mL of triethylamine is slowly added with stirring, at room temperature. The resulting black reaction mixture is stirred for 45 minutes at room temperature. Methanol is removed *in vacuo* and the residue taken up in 700 mL of ethyl acetate. The mixture is filtered through celite and washed sequentially with saturated sodium bicarbonate (3X150 mL), water (1X150 mL), 1N potassium bisulfate (3x150 mL) and brine (1X150 mL). The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:1 hexanes:ethyl acetate).

EXAMPLE 57

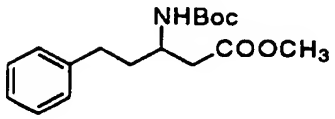
Compound **57**



Compound **57** is prepared using the procedure described for Compound **56**, substituting N-α-Boc-D-alanine.

EXAMPLE 58

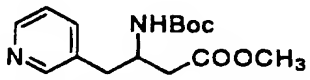
Compound **58**



Compound **58** is prepared using the procedure described for Compound **56**, substituting N α -Boc-D-homophenylalanine.

EXAMPLE 59

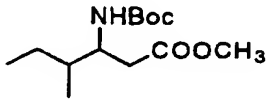
Compound **59**



Compound **59** is prepared using the procedure described for Compound **56**, substituting N-α-Boc-D-3-pyridylalanine.

EXAMPLE 60

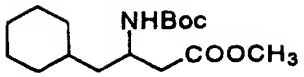
Compound **60**



Compound **60** is prepared using the procedure described for **56**, substituting N-α -Boc-D-isoleucine.

EXAMPLE 61

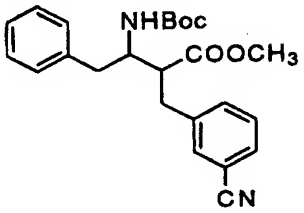
Compound **61**



Compound **61** is prepared using the procedure described for Compound **56**, substituting N-α -Boc-D-cyclohexylalanine.

EXAMPLE 62

Compound **62**

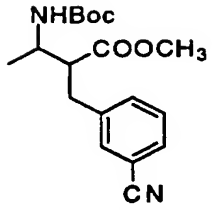


A solution of Compound **56** (11 mmol) in 70 mL of dry tetrahydrofuran is cooled to -78°C and a solution of lithium hexamethyldisilazane in tetrahydrofuran (33 mmol) is added via syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is warmed to -25°C over 40 minutes and recooled to -78°C. A solution of 3-cyanobenzyl bromide (27 mmol) in 20 mL of tetrahydrofuran is added vi syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is allowed to come to room temperature and stirred at room temperature for 1 hour.

125 mL of saturated sodium bicarbonate is added and tetrahydrofuran is removed *in vacuo*. The remaining material is partitioned between 500 mL of ethyl acetate and 150 mL of saturated sodium bicarbonate. The organic phase is further washed with saturated sodium bicarbonate (2x100 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo. The residue is triturated with 40 mL of 4:1 hexanes:ethyl acetate. The solid material is filtered off and discarded. The filtrate, containing the desired product, is concentrated *in vacuo*.

EXAMPLE 63

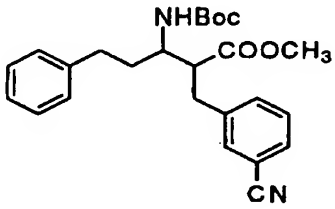
Compound **63**



Compound **63** is prepared following the method described for Compound **62**, substituting the product obtained in Example 57.

EXAMPLE 64

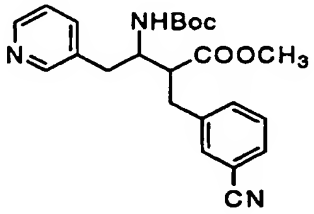
Compound **64**



Compound **64** is prepared following the method described for Compound **62**, substituting the product obtained in Example 58.

EXAMPLE 65

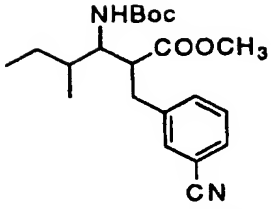
Compound **65**



Compound 65 is prepared following the method described for Compound **62**, substituting the product obtained in Example **59**.

EXAMPLE 66

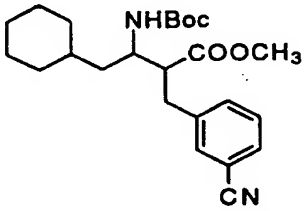
Compound **66**



Compound 66 is prepared following the method described for Compound **62**, substituting the product obtained in Example 60.

EXAMPLE 67

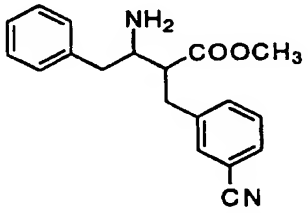
Compound **67**



Compound **67** is prepared following the method described for Compound **62**, substituting the product obtained in Example 61.

EXAMPLE 68

Compound **68**



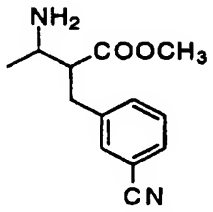
To a solution of Compound **62** (5 mmol) in 60 mL of methylene chloride is added 20 mL of trifluoroacetic acid, dropwise at 0°C. The resulting solution is stirred for 2 hour at 0°C. Solvents are removed *in vacuo* and the residue purified by reverse phase HPLC using a gradient of 30% to 70% acetonitrile in water containing 0.1% trifluoroacetic acid.

Acetonitrile is removed in vacuo and the remaining material partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous layer is extracted twic

with ethyl acetate and the combined organic layers are dried over magnesium sulfate filtered, and concentrated in vacuo.

EXAMPLE 69

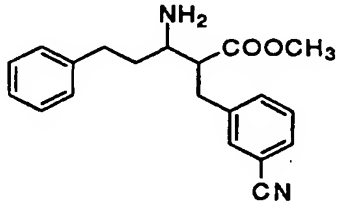
Compound **69**



Compound **69** is prepared according to the method described in Example **68**, substituting the product obtained in Example **63**.

EXAMPLE 70

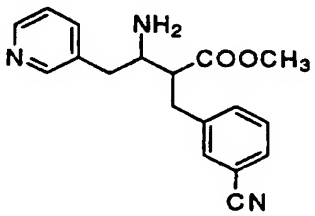
Compound **70**



Compound **70** is prepared according to the method described in Example 68, substituting the product obtained in Example 64.

EXAMPLE 71

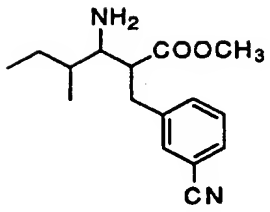
Compound **71**



Compound **71** is prepared according to the method described in Example 68, substituting the product obtained in Example **65**.

EXAMPLE 72

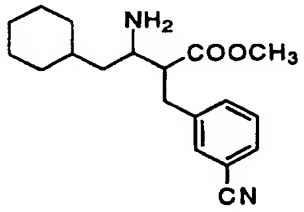
Compound **72**



Compound **72** is prepared according to the method described in Example 68, substituting the product obtained in Example **66**.

EXAMPLE 73

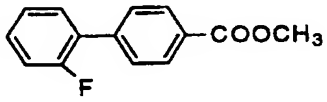
Compound **73**



Compound **73** is prepared according to the method described in Example 68, substituting the product obtained in Example **67**.

EXAMPLE 74

Compound **74**



Solution (A): To a solution of 11.8 mL of n-butyl lithium in hexanes (19 mmol) in 13 mL of tetrahydrofuran is added a solution of 1-bromo-2-fluorobenzene (19 mmol) in 2 mL of tetrahydrofuran, dropwise via syringe at -78°C. Stirring at -78 °C is continued for 1 hour. A solution of zinc chloride (19 mmol) in 38 mL of tetrahydrofuran is added over 2 minutes at -78°C. The resulting solution is allowed to come to room temperature over 40 minutes.

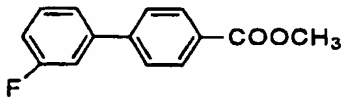
Solution (B): To a solution of bis(triphenylphosphine) palladium dichloride (1 mmol) in 11 mL of tetrahydrofuran is added diisobutyl aluminum hydride (1 mmol) as a

solution in hexanes, at room temperature, followed by methyl iodobenzoate(16 mmol in a single portion at room temperature.

Solution (A) is added to solution (B) and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture is diluted with 300 mL of diethyl ether and washed with 1N hydrochloric acid (3x75 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated in vacuo.

EXAMPLE 75

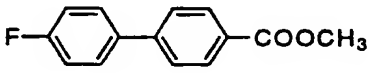
Compound **75**



Compound **75** is prepared according to the method described for Compound **74**, substituting 1-bromo-3-fluorobenzene in the preparation of Solution (A).

EXAMPLE 76

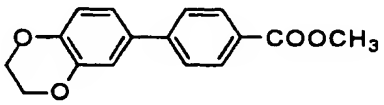
Compound **76**



Compound **76** is prepared according to the method described for Compound **74**, substituting 1-bromo-4-fluorobenzene in the preparation of Solution (A).

EXAMPLE 77

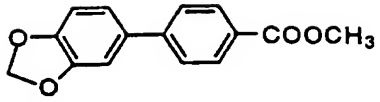
Compound **77**



Compound **77** is prepared according to the method described in EXAMPLE 74, substituting 3,4-ethylenedioxy bromobenzene in the preparation of Solution (A).

EXAMPLE 78

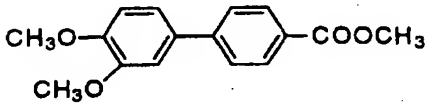
Compound **78**



Compound **78** is prepared according to the method described in EXAMPLE 74, substituting 3,4-methylenedioxy bromobenzene in the preparation of Solution (A).

EXAMPLE 79

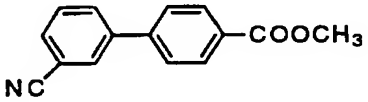
Compound **79**



Compound **79** is prepared according to the method described in Example 74, substituting 3,4-dimethoxy bromobenzene in the preparation of Solution (A).

EXAMPLE 80

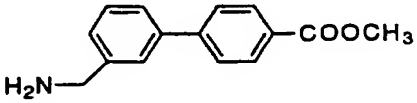
Compound **80**



Compound **80** is prepared according to the method described in Example 74, substituting 3-cyano bromobenzene in the preparation of Solution (A).

EXAMPLE 81

Compound **81**

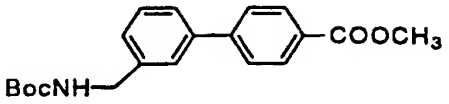


Ammonia gas is bubbled into a suspension of Compound **80** (24 mmol) in 200 mL of methanol for five minutes. To the resulting solution is added rhodium on alumina (5 g and the suspension is shaken under a positive pressure of hydrogen for 36 hours.

Catalyst is filtered off and methanol is removed in vacuo to give an oil which is triturated with ether and filtered.

EXAMPLE 82

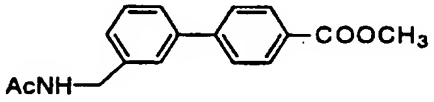
Compound **82**



A solution of Compound **81** (15.4 mmol), triethylamine (17 mmol), di-tert-butyl dicarbonate (15.4 mmol), and 4-dimethylaminopyridine (1.5 mmol) in 60 mL of dimethylformamide is stirred at room temperature overnight. The solution is diluted with 800 mL of ethyl acetate and washed with 1N hydrochloric acid (3x150 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:2 hexanes:ethyl acetate).

EXAMPLE 83

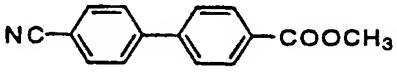
Compound **83**



A solution of Compound **81** (2 mmol), acetic anhydride (8 mmol), and dimethylamino pyridine (0.2 mmol) in 20 mL of pyridine is stirred at room temperature overnight. The reaction mixture is poured into 200 mL of 5% hydrochloric acid and extracted with ethyl acetate (3x200 mL). The combined organic extracts are dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:1 hexanes:ethyl acetate).

EXAMPLE 84

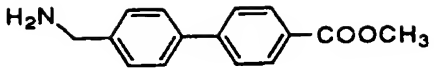
Compound **84**



Compound **84** is prepared according to the method described for Compound **74**, substituting 4-cyano bromobenzene in the preparation of Solution (A).

EXAMPLE 85

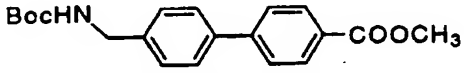
Compound **85**



Compound **85** is prepared according to the method described for Compound **81**, substituting the product obtained in Example **84**.

EXAMPLE 86

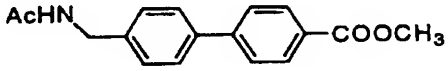
Compound **86**



Compound **86** is prepared according to the method described for Compound **82**, substituting the product obtained in Example 85.

EXAMPLE 87

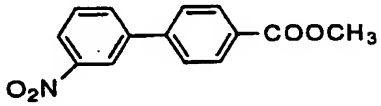
Compound **87**



Compound **87** is prepared according to the method described for Compound **83**, substituting the product obtained in Example **85**.

EXAMPLE 88

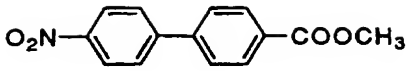
Compound **88**



To a solution of methyl coumalate (6.5 mmol) and 3-nitrostyrene (32.5 mmol) in 30 ml of m-xylene is added 10% palladium on carbon (2. 5 g) in a single portion. The reaction mixture is heated at 140°C overnight. After cooling, the reaction mixture is filtered through celite and the filtrate concentrated *in vacuo*. The resulting slurry is triturated with 3:1 hexanes:ethyl acetate. The solid, which is the desired product, is removed by filtration.

EXAMPLE 89

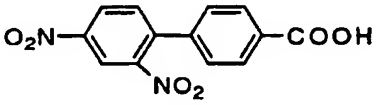
Compound **89**



Compound **89** is prepared using a method identical to the one used for Compound **88**, substituting 4-nitrostyrene.

EXAMPLE 90

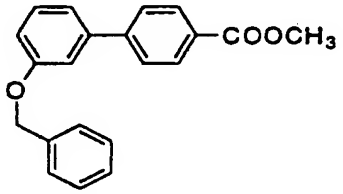
Compound **90**



To a flask containing 100 mL of fuming nitric acid is added 4-biphenyl carboxylic acid (20 mmol), portionwise at 0°C. Stirring is continued 15 minutes at 0°C. Water (100 mL) is slowly added and the filtrate collected and recrystallized from ethanol.

EXAMPLE 91

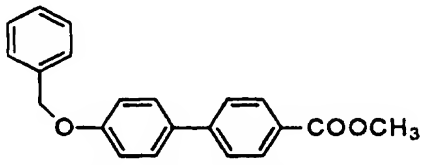
Compound **91**



Compound **91** is prepared according to the method described for Compound **74**, substituting 3-benzyloxy bromobenzene in the preparation of Solution (A).

EXAMPLE 92

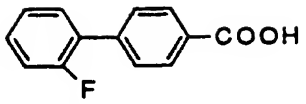
Compound **92**



Compound **92** is prepared according to the method described for Compound **74**, substituting 4-benzyloxy bromobenzene in the preparation of Solution (A).

EXAMPLE 93

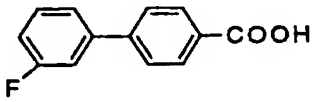
Compound **93**



To a suspension of Compound **74** (1.6 mmol) in 10 mL of methanol and 20 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at room temperature. The resulting solution is allowed to stir at room temperature for 2 hours. Organic solvents are removed in vacuo and the residue diluted with 20 mL of water and brought to pH 2 with 1N hydrochloric acid. Solid material is filtered off and dried under vacuum.

EXAMPLE 94

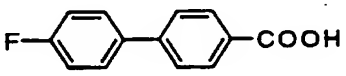
Compound **94**



Compound **94** is prepared according to the method described for **93**, substituting the product obtained in Example **75**.

EXAMPLE 95

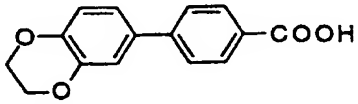
Compound **95**



Compound **95** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 76.

EXAMPLE 96

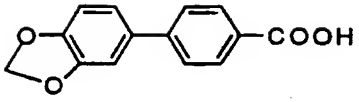
Compound **96**



Compound **96** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 77.

EXAMPLE 97

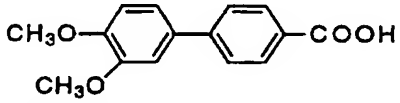
Compound **97**



Compound **97** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 78.

EXAMPLE 98

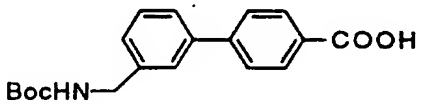
Compound **98**



Compound **98** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 79.

EXAMPLE 99

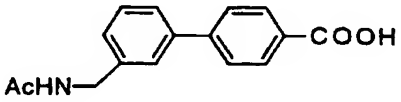
Compound **99**



Compound **99** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 82.

EXAMPLE 100

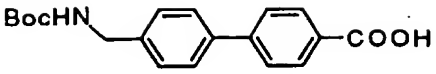
Compound **100**



Compound **100** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 83.

EXAMPLE 101

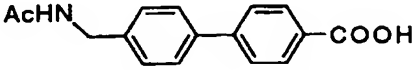
Compound **101**



Compound **101** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 86.

EXAMPLE 102

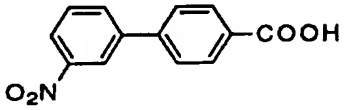
Compound **102**



Compound **102** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 87.

EXAMPLE 103

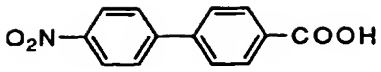
Compound **103**



Compound **103** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 88.

EXAMPLE 104

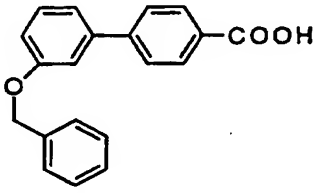
Compound **104**



Compound **104** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 89.

EXAMPLE 105

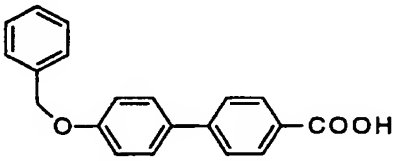
Compound **105**



Compound **105** is prepared according to the method described for Compound **93**, substituting the product obtained in Example 91.

EXAMPLE 106

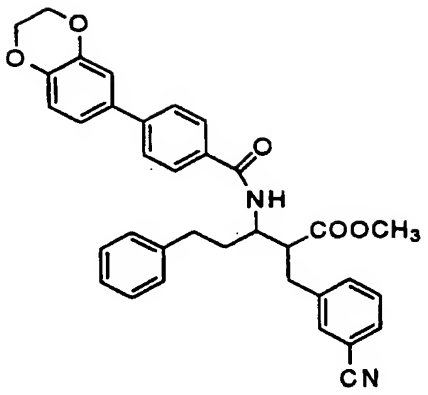
Compound **106**



Compound **106** is prepared according to the method described for Compound **93**, substituting the product obtained in Example **90**.

EXAMPLE 107

Compound **107**

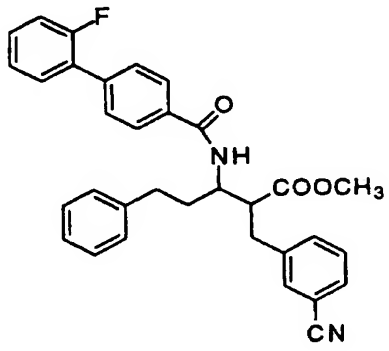


To a solution of Compound **96** (2 mmol) in 10 mL of DMF is added diisopropyl ethylamine (2 mmol) in a single portion at room temperature, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2 mmol) in a similar fashion. The reaction mixture is stirred for 2 minutes at room temperature and a solution of Compound **70** (2 mmol) in 15 mL of dimethylformamide is added in a single portion. Stirring is continued overnight at room temperature.

The reaction mixture is diluted with 300 mL of ethyl acetate and washed sequentially with 1N hydrochloric acid (3x75 mL), water, saturated sodium bicarbonate (3x75 mL) and brine. The organic phase is dried over magnesium sulfate, filtered and concentrated *in vacuo*.

EXAMPLE 108

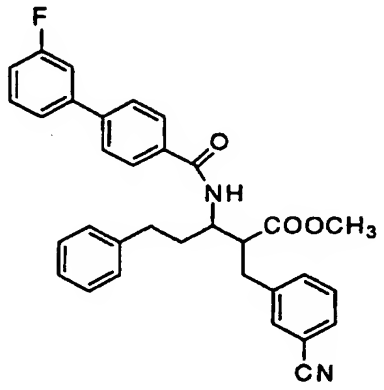
Compound **108**



Compound **108** is prepared using the same procedure described for Compound **107**, substituting Compound **93** for Compound **96**.

EXAMPLE 109

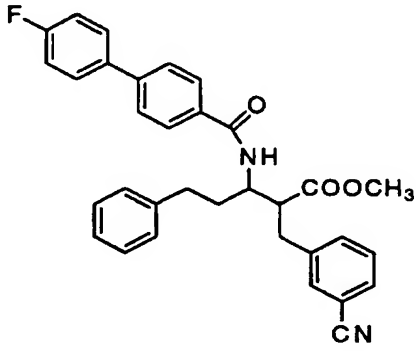
Compound **109**



Compound **109** is prepared using the same procedure described for Compound **107**, substituting Compound **94** for Compound **96**.

EXAMPLE 110

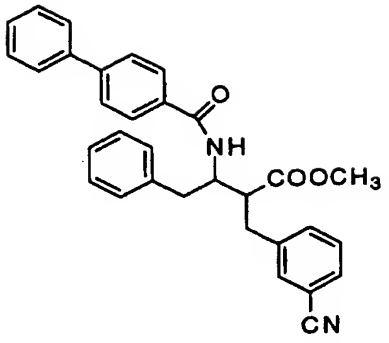
Compound **110**



Compound **110** is prepared using the same procedure described for Compound **107**, substituting Compound **95** for Compound **96**.

EXAMPLE 111

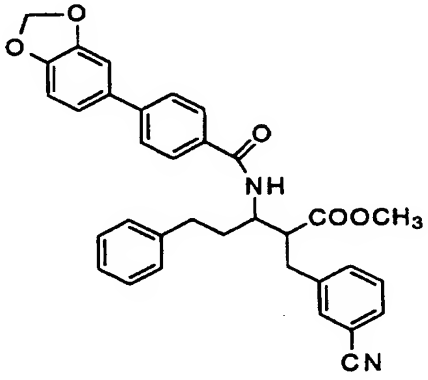
Compound **111**



Compound **111** is prepared using the same procedure described for Compound **107**, substituting 4-biphenyl carboxylic acid for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 112

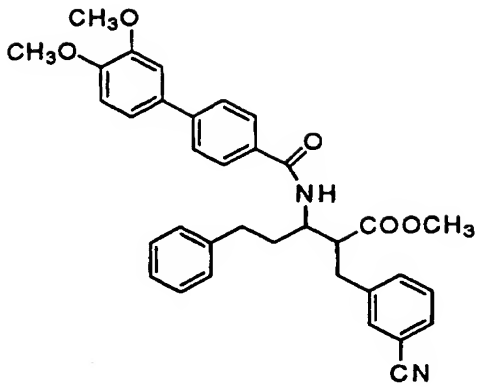
Compound **112**



Compound **112** is prepared using the same procedure described for Compound **107**, substituting Compound **97** for Compound **96**.

EXAMPLE 113

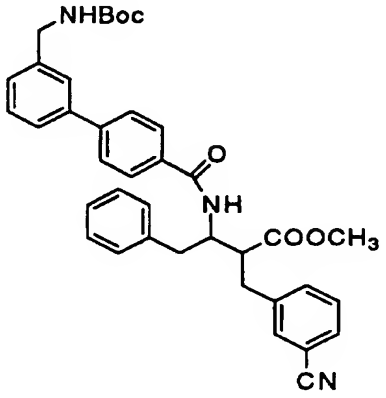
Compound **113**



Compound **113** is prepared using the same procedure described for Compound **107**, substituting Compound **98** for Compound **96**.

EXAMPLE 114

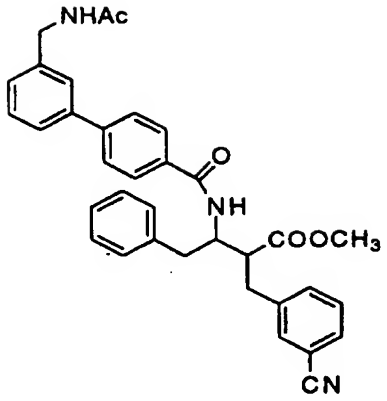
Compound **114**



Compound **114** is prepared using the same procedure described for Compound **107**, substituting Compound **99** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 115

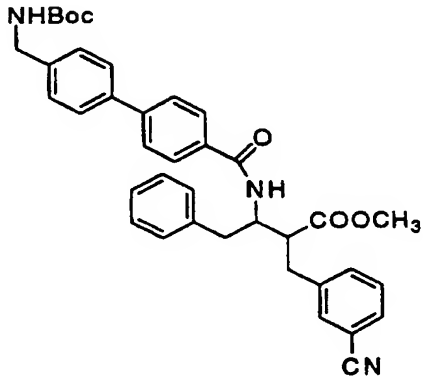
Compound **115**



Compound **115** is prepared using the same procedure described for Compound **107**, substituting Compound **100** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 116

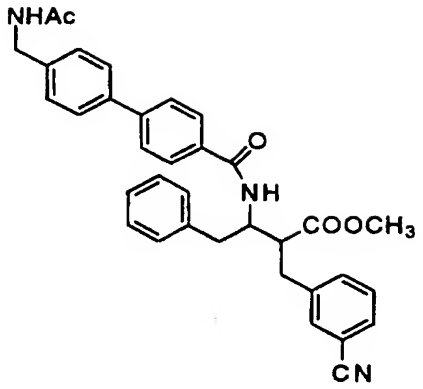
Compound **116**



Compound **116** is prepared using the same procedure described for Compound **107**, substituting Compound **101** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 117

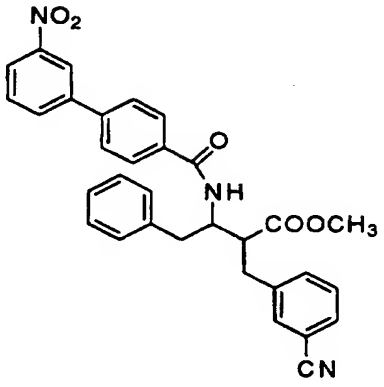
Compound **117**



Compound **117** is prepared using the same procedure described for Compound **107**, substituting Compound **102** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 118

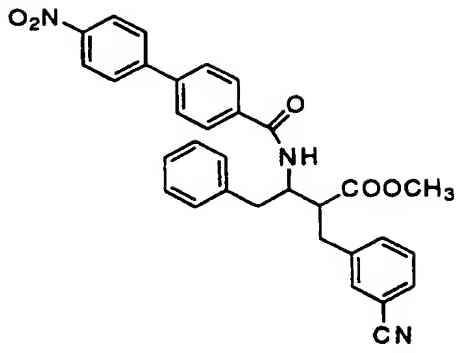
Compound **118**



Compound **118** is prepared using the same procedure described for Compound **107**, substituting Compound **103** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 119

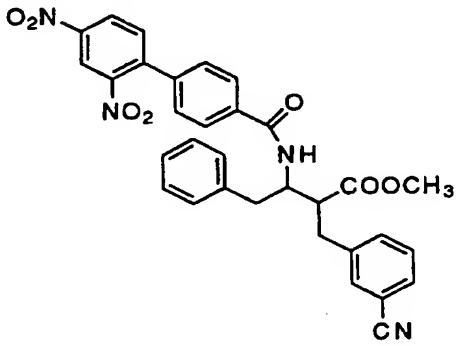
Compound **119**



Compound **119** is prepared using the same procedure described for Compound **107**, substituting Compound **104** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 120

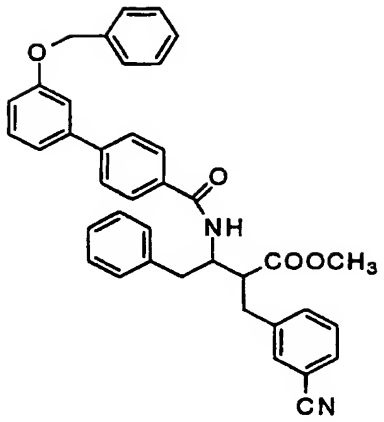
Compound **120**



Compound **120** is prepared using the same procedure described for Compound **107**, substituting Compound **90** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 121

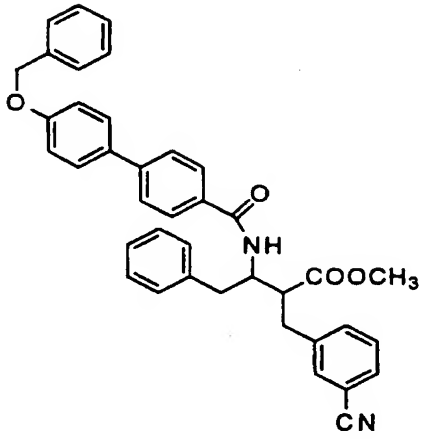
Compound **121**



Compound **121** is prepared using the same procedure described for Compound **107**, substituting Compound **105** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 122

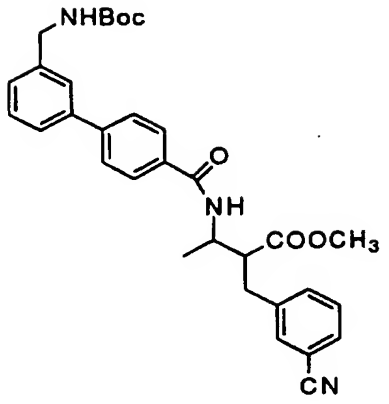
Compound **122**



Compound **122** is prepared using the same procedure described for Compound **107**, substituting Compound **106** for Compound **96** and substituting Compound **68** for Compound **70**.

EXAMPLE 123

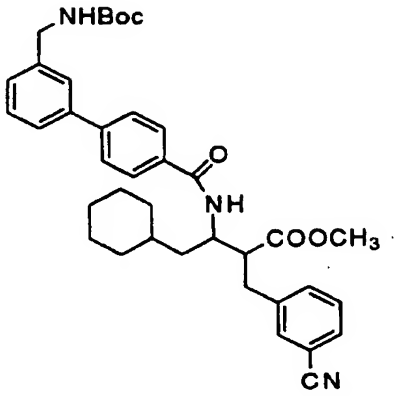
Compound **123**



Compound **123** is prepared using the same procedure described for Compound **107**, substituting Compound **99** for **96** and substituting Compound **69** for Compound **70**.

EXAMPLE 124

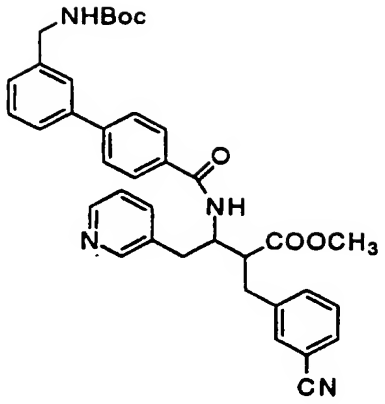
Compound **124**



Compound **124** is prepared using the same procedure described for Compound **107**, substituting Compound **99** for Compound **96** and substituting Compound **73** for Compound **70**.

EXAMPLE 125

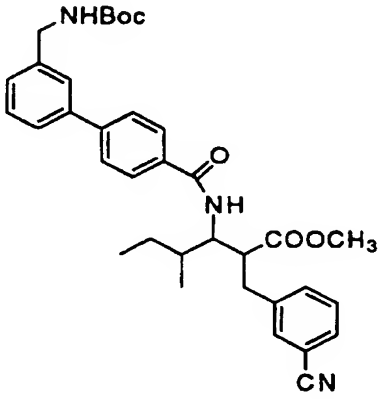
Compound **125**



Compound **125** is prepared using the same procedure described for Compound **107**, substituting Compound **99** for Compound **96** and substituting Compound **71** for Compound **70**.

EXAMPLE 126

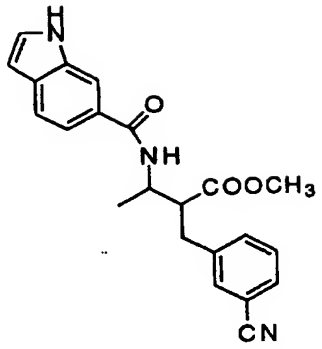
Compound **126**



Compound **126** is prepared using the same procedure described for Compound **107**, substituting Compound **99** for Compound **96** and substituting Compound **72** for Compound **70**.

EXAMPLE 127

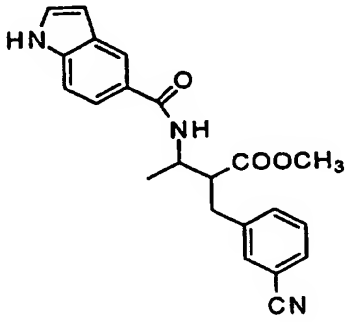
Compound **127**



Compound **127** is prepared using the same procedure described for Compound **107**, substituting indole-6-carboxylic acid for Compound **96** and substituting Compound **69** for Compound **70**.

EXAMPLE 128

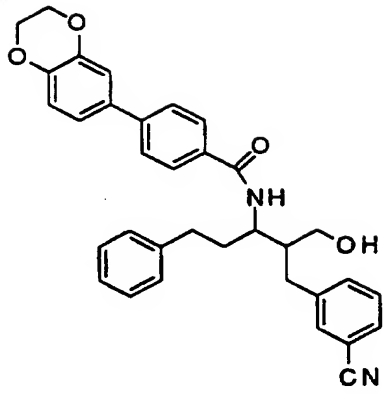
Compound **128**



Compound **128** is prepared using the same procedure described for Compound **107**, substituting indole-5-carboxylic acid for Compound **96** and substituting Compound **69** for Compound **70**.

EXAMPLE 129

Compound **129**

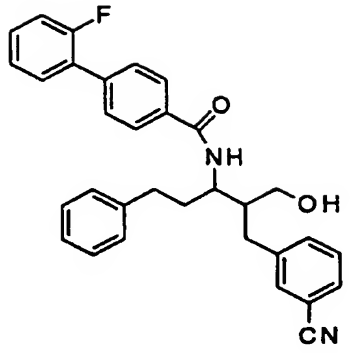


To a solution of Compound **107** (1.2 mmol) in 10 mL of methanol and 10 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at 0°C. The solution is allowed to come to room temperature and stirred at room temperature for 2.5 hours. The solution is cooled to 0°C and 1N hydrochloric acid is added until the pH is 7. Organic solvents are removed *in vacuo* and the residue diluted with 25 mL o water. 1N hydrochloric acid is added to bring the pH down to 2 and the mixture is extracted with ethyl acetate (3x75 mL). The combined organic extracts are dried ovei magnesium sulfate, filtered, concentrated, and dried under vacuum.

The acid (1.1 mmol) is dissolved in 15 mL of tetrahydrofuran and cooled to -20°C. N-methyl morpholine (1.45 mmol) is added in a single portion, followed by isobutyl chloroformate (1.45 mmol) dropwise via syringe. The reaction mixture is allowed to stir at -20°C for 20 minutes. The reaction mixture is filtered into a solution of sodium borohydride (11 mmol) in 20 mL of water at 0°C. Stirring is continued 1.5 hours at 0°C. The reaction mixture is diluted with 300 mL of ethyl acetate and washed with water (3x100 mL) and brine. The organic phase is dried over magnesium sulfate, filtered, and concentrated. The resulting alcohol is purified by flash chromatography (2:3 ethyl acetate:hexanes).

EXAMPLE 130

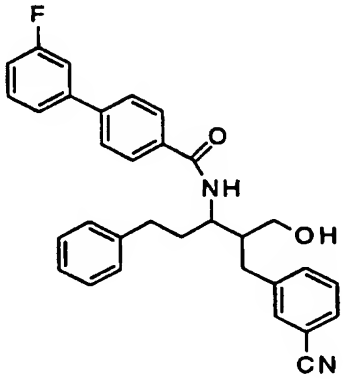
Compound **130**



Compound **130** is prepared following the procedure described for Compound **129**, substituting Compound **108** for Compound **107**.

EXAMPLE 131

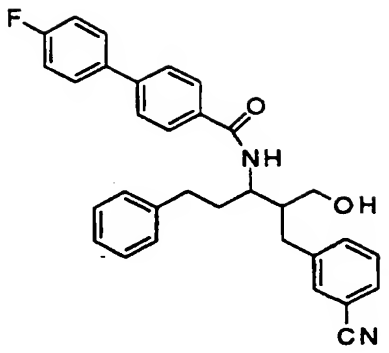
Compound **131**



Compound **131** is prepared following the procedure described for Compound **129**, substituting Compound **109** for Compound **107**.

EXAMPLE 132

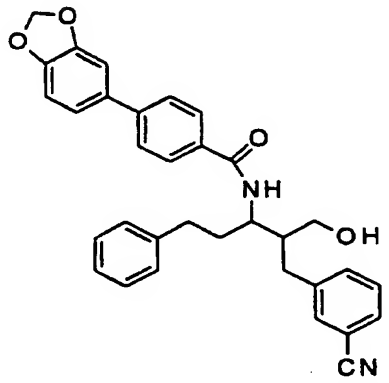
Compound **132**



Compound **132** is prepared following the procedure described for Compound **129**, substituting Compound **110** for Compound **107**.

EXAMPLE 133

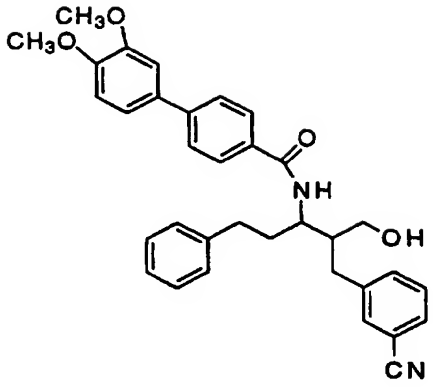
Compound **133**



Compound **133** is prepared following the procedure described for Compound **129**, substituting Compound **112** for Compound **107**.

EXAMPLE 134

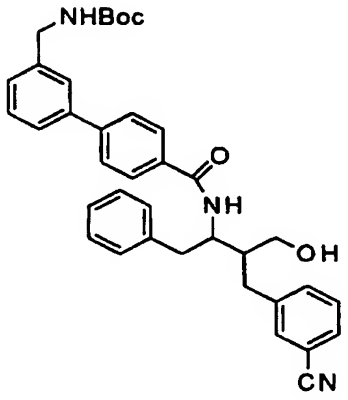
Compound **134**



Compound **134** is prepared following the procedure described for Compound **129**, substituting Compound **113** for Compound **107**.

EXAMPLE 135

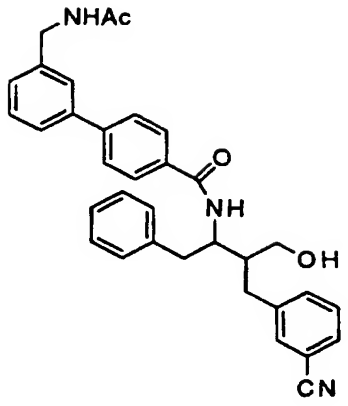
Compound **135**



Compound **135** is prepared following the procedure described for Compound **129**, substituting Compound **114** for Compound **107**.

EXAMPLE 136

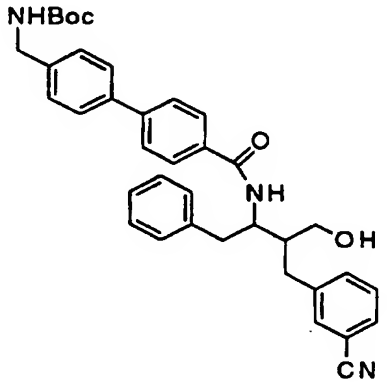
Compound **136**



Compound **136** is prepared following the procedure described for Compound **129**, substituting Compound **115** for Compound **107**.

EXAMPLE 137

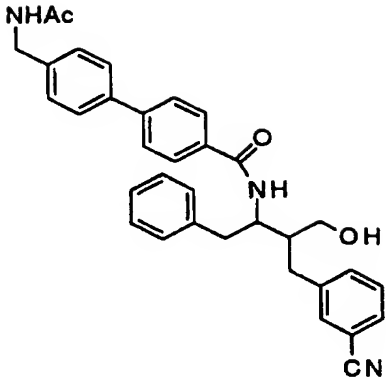
Compound **137**



Compound **137** is prepared following the procedure described for Compound **129**, substituting Compound **116** for Compound **107**.

EXAMPLE 138

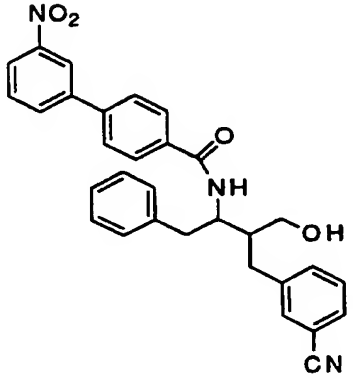
Compound **138**



Compound **138** is prepared following the procedure described for Compound **129**, substituting Compound **117** for Compound **107**.

EXAMPLE 139

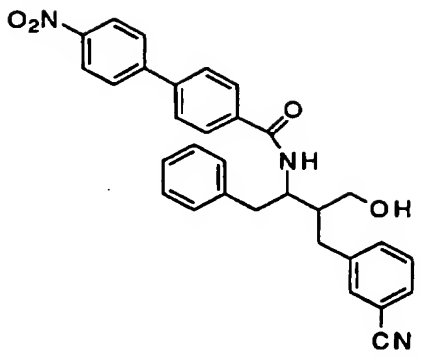
Compound **139**



Compound **139** is prepared following the procedure described for Compound **129**, substituting Compound **118** for Compound **107**.

EXAMPLE 140

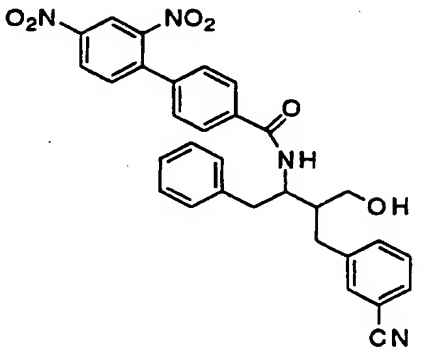
Compound **140**



Compound **140** is prepared following the procedure described for Compound **129**, substituting Compound **119** for Compound **107**.

EXAMPLE 141

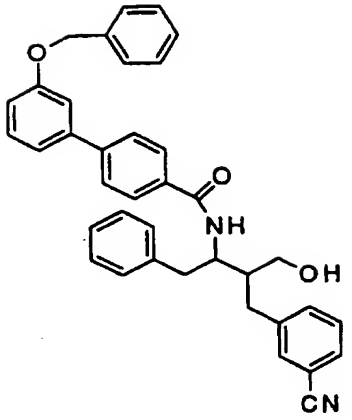
Compound **141**



Compound **141** is prepared following the procedure described for Compound **129**, substituting Compound **120** for Compound **107**.

EXAMPLE 142

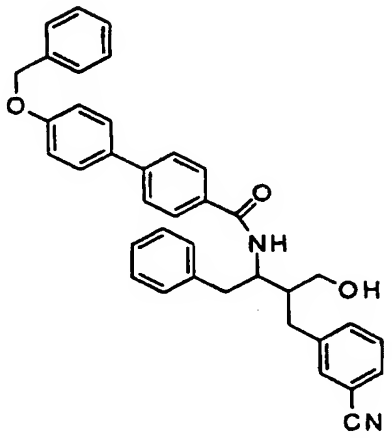
Compound **142**



Compound **142** is prepared following the procedure described for Compound **129**, substituting Compound **121** for Compound **107**.

EXAMPLE 143

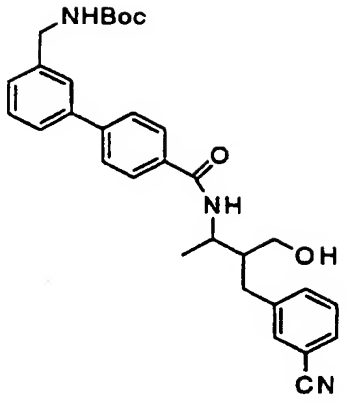
Compound **143**



Compound **143** is prepared following the procedure described for Compound **129**, substituting Compound **122** for Compound **107**.

EXAMPLE 144

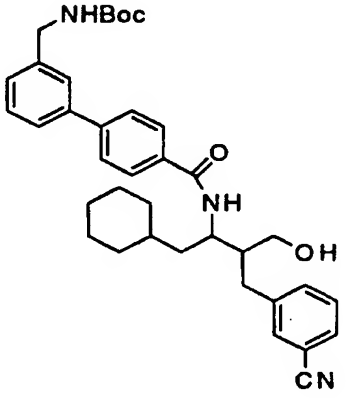
Compound **144**



Compound **144** is prepared following the procedure described for Compound **129**, substituting Compound **123** for Compound **107**.

EXAMPLE 145

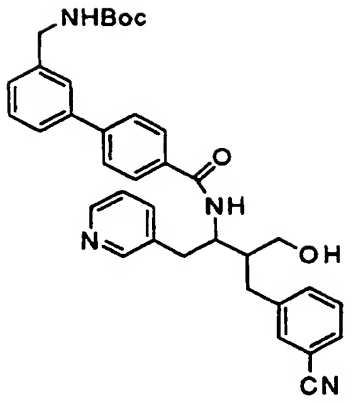
Compound **145**



Compound **145** is prepared following the procedure described for Compound **129**, substituting Compound **124** for Compound **107**.

EXAMPLE 146

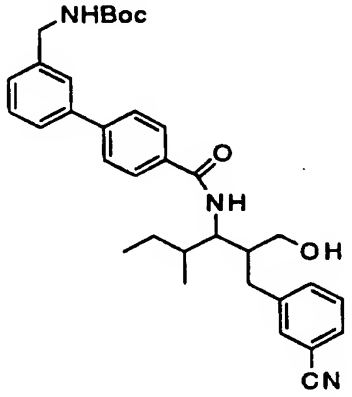
Compound **146**



Compound **146** is prepared following the procedure described for Compound **129**, substituting Compound **125** for Compound **107**.

EXAMPLE 147

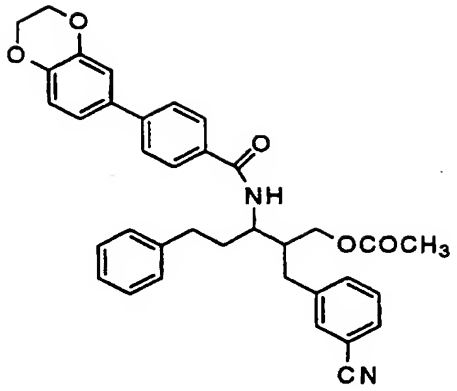
Compound **147**



Compound **147** is prepared following the procedure described for Compound **129**, substituting Compound **126** for Compound **107**.

EXAMPLE 148

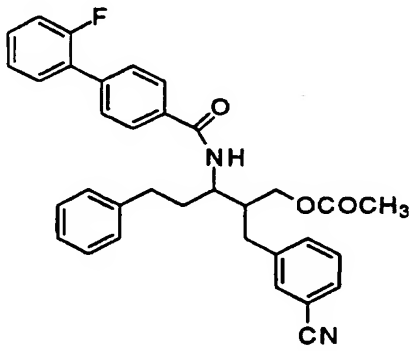
Compound **148**



To a solution of Compound **129** (0.5 mmol) in 8 mL of methylene chloride is added pyridine (0.6 mmol) in a single portion at 0°C. Acetic anhydride (0.6 mmol) is added in a single portion, followed by dimethylaminopyridine in a similar fashion. The reaction mixture is allowed to come to room temperature and stirring is continued overnight. The reaction mixture is partitioned between 10 mL of 0.1N hydrochloric acid and 30 mL of methylene chloride. The organic layer is dried over sodium sulfate filtered and concentrated *in vacuo*.

EXAMPLE 149

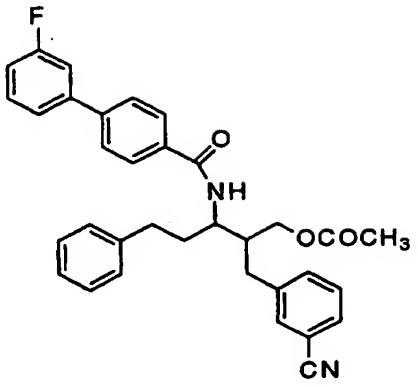
Compound **149**



Compound **149** is prepared following the method described for Compound **148**, substituting Compound **130** for Compound **129**.

EXAMPLE 150

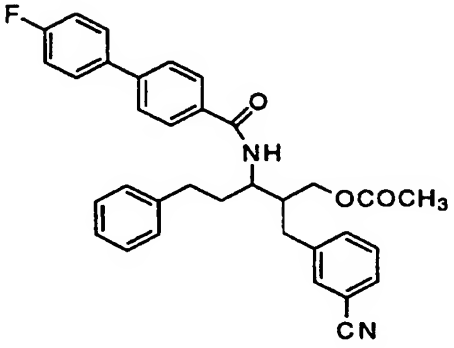
Compound **150**



Compound **150** is prepared following the method described for Compound **148**, substituting Compound **131** for Compound **129**.

EXAMPLE 151

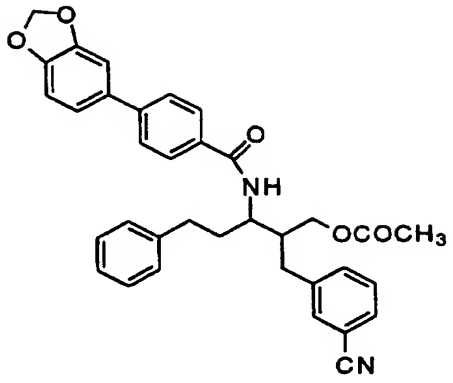
Compound **151**



Compound **151** is prepared following the method described for Compound **148**, substituting Compound **132** for Compound **129**.

EXAMPLE 152

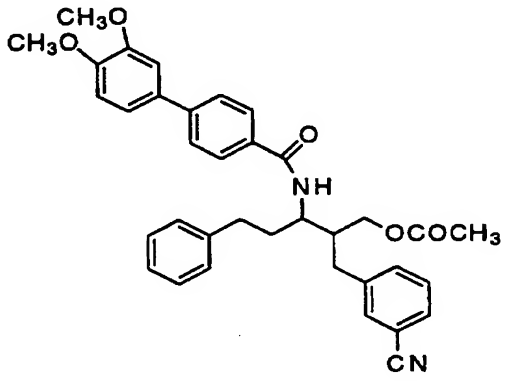
Compound **152**



Compound **152** is prepared following the method described for Compound **148**, substituting Compound **133** for Compound **129**.

EXAMPLE 153

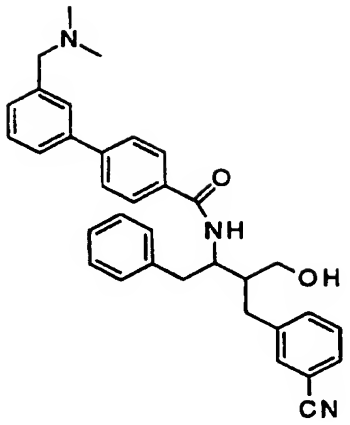
Compound **153**



Compound **153** is prepared following the method described for Compound **148**, substituting Compound **134** for Compound **129**.

EXAMPLE 154

Compound **154**

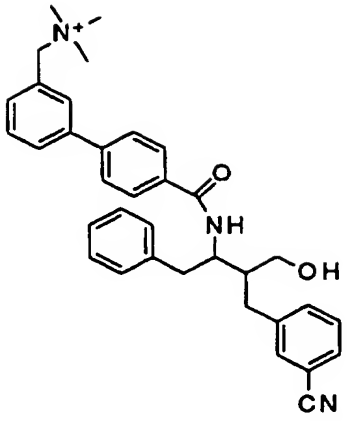


To a solution of Compound **135** (1.1 mmol) in 30 mL of methylene chloride is added 10 mL of trifluoroacetic acid in a single portion at 0°C. The resulting solution is stirre for 3 hours at 0°C. Solvents are removed *in vacuo* and the residue partitioned between 10% aqueous sodium bicarbonate and ethyl acetate. The organic phase is dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The free amine (1.1 mmol) is dissolved in 10 mL of glacial acetic acid and paraformaldehyde (11 mmol) is added in a single portion at room temperature. Stirring is continued overnight at room temperature.

The reaction mixture is poured into 50 mL of ice cold 2N sodium hydroxide and extracted with ethyl acetate (3x100 mL). The combined organic extracts are backwashed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo. The desired product is purified by reverse phase HPLC using a gradient of 20% to 100% acetonitrile in water, buffered with 0.1% trifluoroacetic acid.

EXAMPLE 155

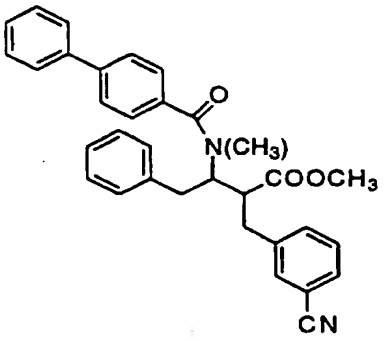
Compound **155**



To a solution of Compound **154** (0.5 mmol) in 10 mL of dry acetone is added methyl iodide (large excess, 2 mL) in a single portion at room temperature. The resulting solution is allowed to stir at room temperature overnight. Solvents are removed in vacuo to provide the desired tetramethylammonium salt.

EXAMPLE 156

Compound **156**

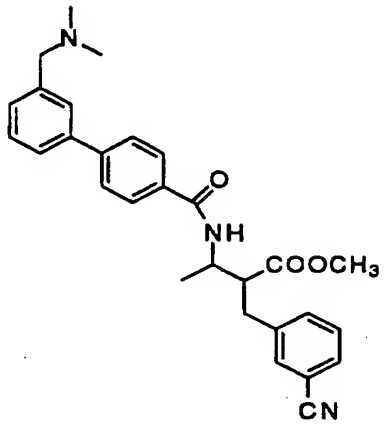


To a solution of Compound **111** (0.8 mmol) in 2 mL of dimethylformamide and 8 mL c tetrahydrofuran is added sodium hydride (1 mmol) in a single portion at 0°C. The solution is stirred for 1 hour at 0°C and methyl iodide (large excess) is added in a single portion. The solution is allowed to come to room temperature and stirred overnight. The reaction mixture is poured into 100 mL of ice water and extracted with ethyl acetate (3x75 mL). The combined organic extracts are backwashed with water,

dried over magnesium sulfate, filtered, conc ntrated in vacuo, and purified by flash chromatography (1:2 ethyl acetate:hexanes).

EXAMPLE 157

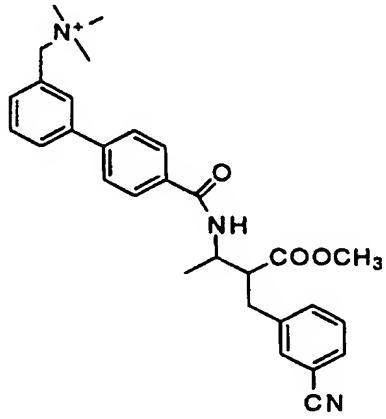
Compound **157**



Compound **157** is prepared following the procedure described for Compound **154**, substituting Compound **123** for **135**.

EXAMPLE 158

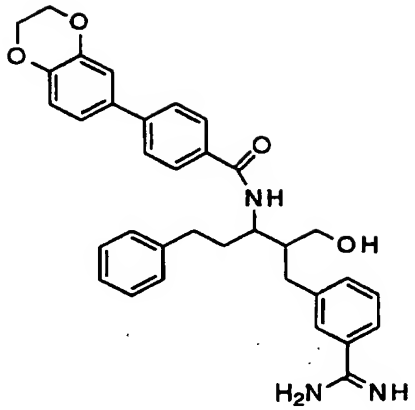
Compound **158**



Compound **158** is prepared according to the method described for Compound **155**, starting from Compound **157**.

EXAMPLE 159a

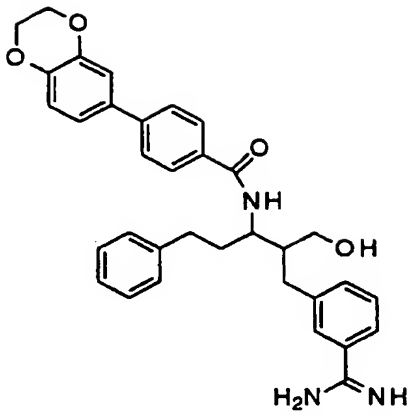
Compound **159**



To a solution of Compound **129** (1 mmol) in 50 mL of dry methanol is added crushed 3Å molecular sieves (approximately 1g). The mixture is stirred for 10 minutes at 0°C and hydrogen chloride gas is bubbled through the reaction mixture for 10 minutes at 0°C. The reaction mixture is allowed to come to room temperature and stirred overnight. Nitrogen gas is bubbled through the reaction mixture for 5 minutes and methanol is removed *in vacuo*. The residue is dried under vacuum to remove all traces of hydrogen chloride, then remixed with 75 mL of dry methanol. The mixture is then cooled to 0°C and ammonia gas is bubbled through the reaction mixture for 10 minutes. The reaction mixture is allowed to come to room temperature, then heated a 60°C for 3 hours. After cooling to room temperature, nitrogen gas is bubbled through the reaction for 5 minutes and the mixture is filtered through celite, concentrated *in vacuo*, and purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed *in vacuo* and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

EXAMPLE 159b

Compound **159**



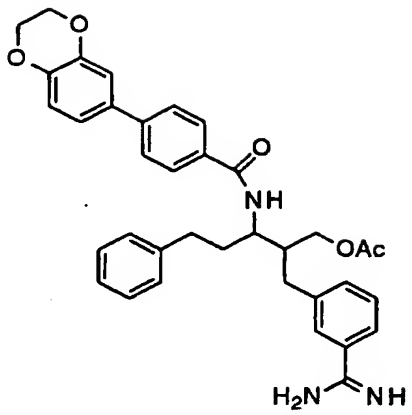
1H NMR (300 Mhz, d6 DMSO) d 9.21 (s, 2H), 9.01 (s, 2H), 8.22 (d, 1H, J=9.6 Hz), 7.85 (d, 2H,J=7.2 Hz), 7.70 (d, 2H, J=7.2 Hz), 7.62-7.38 (m, 4H), 7.25-7.05 (m, 7H), 6.93 (d, 1H, J=8.4 Hz), 4.90-4.65 (m, 1H), 4.24 (s, 4H), 4.18-4.05 (m, 2H), 2.78-2.63 (m, 2H), 2.65-2.45 (m, 2H), 2.08-1.75 (m,3H).
MS, LRFAB, calc.591, found 592 (M+H)+.

Into a solution of Compound **129** (1 mmol) in 20 mL of pyridine and 4 mL of triethylamine is bubbled hydrogen sulfide for 10 minutes at room temperature. The solution is allowed to stir at room temperature overnight. Nitrogen gas is bubbled through the reaction for 5 minutes and solvents are removed *in vacuo*. The residue is dried under vacuum, then dissolved in 15 mL of dry acetone. To this solution is adde 5 mL of methyl iodide and this solution is heated at 50°C for 1 hour, then concentrated *in vacuo*. The residue is dissolved in 20 mL of methanol and ammonium acetate (2 mmol) is added in a single portion at room temperature. The reaction mixture is heated at 65°C for 2 hours. After cooling, methanol is removed in vacuo and the residue purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed *in vacuo* and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

The following compounds are prepared from the appropriate starting materials by procedures substantially similar to the procedures described above.

EXAMPLE 161

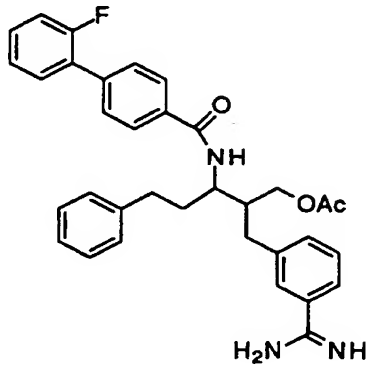
Compound **161**



1H NMR (300 MHz, d6 DMSO) d 9.23 (s, 2H), 9.01 (s, 2H), 8.27 (d, 1H, J=9.6 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.72 (d, 2H, J=7.2 Hz), 7.65-7.55 (m, 2H), 7.54-7.42 (m, 2H), 7.28-7.08 (m, 7H), 6.94 (d, 1H, J=8.4 Hz), 4.25 (s, 4H), 4.24-4.11 (m,1H), 4.05-3.83 (m,2H), 2.86 (dd, 1H, J=6.0, 15.6 Hz), 2.70-2.55 (m, 2H), 2.53-2.43 (m,1H), 2.35-2.20 (m,1H), 1.98-1.90 (m ,2H), 1.87 (s, 3H).
MS, LRFAB, calc.591, found 592 (M+H)+.

EXAMPLE 162

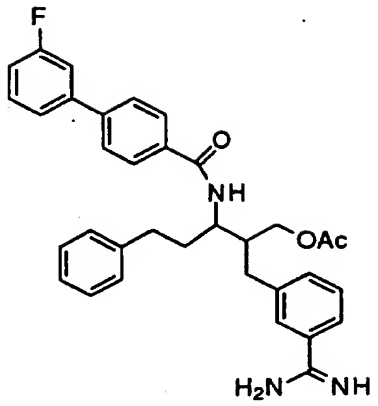
Compound **162**



1H NMR (300 Mhz, d6 DMSO) d 9.21 (s, 2H), 9.01 (s, 2H), 8.22 (d, 1H, J=9.6 Hz), 7.85 (d, 2H,J=7.2 Hz), 7.70 (d, 2H, J=7.2 Hz), 7.62-7.38 (m, 4H), 7.25-7.05 (m, 7H), 6.93 (d, 1H, J=8.4 Hz), 4.90-4.65 (m, 1H), 4.24 (s, 4H), 4.18-4.05 (m, 2H), 2.78-2.63 (m, 2H), 2.65-2.45 (m, 2H), 2.08-1.75 (m,3H).
MS, LRFAB, calc.591, found 592 (M+H)+.

EXAMPLE 163

Compound **163**

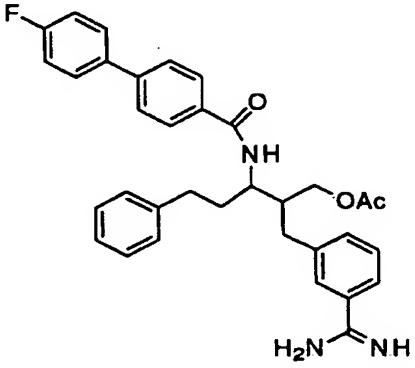


NMR 300 MHz, d6 DMSO, d 9.23 (s, 2H), 9.09 (s, 2H), 8.83 (d, 1H, J=9.6 Hz), 7.97 (d, 2H, J=7.2 Hz), 7.83 (d, 1H, J=7.2 Hz), 7.65-7.35 (m, 7H), 7.28-7.05 (m, 6H), 4.26-4.10 (m,1H), 4.05-3.83 (m, 2H), 2.87 (dd, 1H, J=6.0 Hz,15.6 Hz), 2.70-2.55 (m, 2H), 2.32-2.18 (m, 1H), 2.03-1.90 (m, 2H), 1.87(s, 3H).

MS ion spray: calc. 551, found 552 (M+H)+.

EXAMPLE 164

Compound **164**

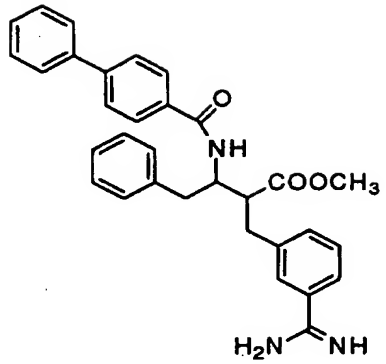


NMR 300 MHz, d6 DMSO, d 9.22 (s, 2H), 9.02 (s, 2H), 8.32 (d, 1H, J=9.6 Hz), 7.96 (d, 2H, J=7.2 Hz), 7.81-7.65 (m, 4H), 7.65-7.40 (m, 4H), 7.38-7.05 (m, 7H), 4.25-4.10 (m, 1H), 4.05-3.85 (m, 2H), 2.87 (dd, 1H, J=6.0,15.6Hz), 2.70-2.55 (m, 2H), 2.54-2.43 (m, 1H), 2.35-2.20 (m, 1H), 1.98-1.90 (m, 2H),1.89 (s, 3H).

MS ion spray: calc. 551, found 552 (M+H)+.

EXAMPLE 165

Compound **165**

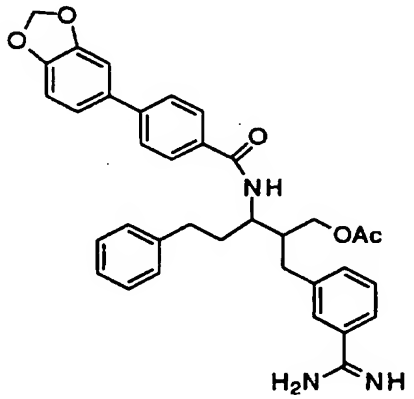


H1 NMR, 300 MHz, d6 DMSO, d 9.25 (s, 2H), 9.18 (s, 2H), 8.35 (d, 1H, J=9.6 Hz), 7.80 (d, 2H, 7.2 Hz), 7.73 (d, 2H, J=7.2 Hz), 7.68 (d, 2H, J=6.0 Hz), 7.62 (br.s, 2H), 7.55-7.31 (m, 5H), 7.25-7.03 (m, 5H), 4.65-4.45 (m, 1H),3.53 (s, 3H), 3.20-2.82 (m, 5H).

MS LRFAB: cal'd 505, found 506 (M+H)+.

EXAMPLE 166

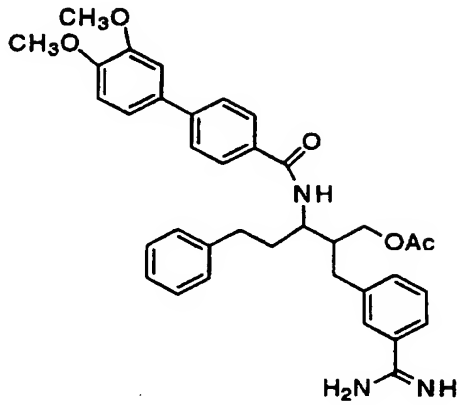
Compound **166**



1H NMR (300 MHz, d6 DMSO) d 9.23 (s, 2H), 8.99 (s, 2H), 8.26 (d, 1H, J=9.6 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.72 (d, 2H, J=7.2 Hz), 7.65-7.56 (m, 2H), 7.54-7.42 (m, 2H), 7.32 (d, 1H, J=2.4 Hz), 7.28-7.08 (m, 6H), 7.02 (d, 1H, J=8.4 Hz), 6.07 (s, 2H), 4.25-4.12 (m, 1H), 4.06-3.85 (m, 2H), 2.85 (dd, 1H, J=6.0, 15.6 Hz),

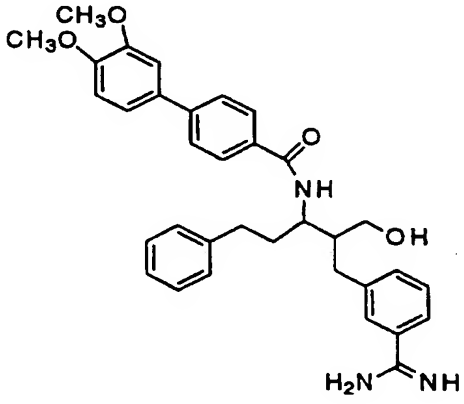
2.68-2.55 (m, 2H), 2.53-2.43 (m, 1H), 2.32-2.20 (m, 1H), 2.01-1.90 (m, 2H), 1.87 (s, 3H).
MS, LRFAB, calc.557, found 558 (M+H)+.

EXAMPLE 167
Compound **167**



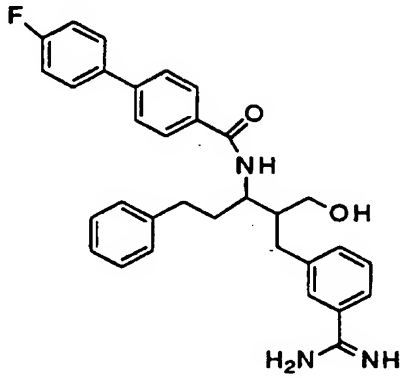
NMR: 9.5 (s, 1H), 9.4 (s, 1H), 8.4 (d, 1H J=9.0 Hz), 8.1 (d, 2H, J=8.0 Hz), 7.9 (d, 2H, J=8.0 Hz), 7.5-7.8 (m, 5H), 7.1-7.4 (m, 7H), 5.0 (m, 1H), 4.0-4.1 (m, 1H), 4.0 (s, 3H), 3.
(s, 3H), 3.6 (m, 1H), 2.9-3.1 (m, 4H), 2.1-2.3 (m, 2H), 2.0 (s, 3H).
M.S. Cal'd 594.3, Found 594.

EXAMPLE 168
Compound **168**



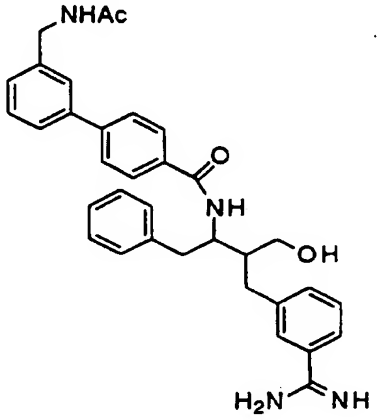
NMR: 9.4 (s, 1H), 9.0 (s, 1H), 8.4 (d, 1H, J=9.0 Hz), 8.1 (d, 2H, J=7.0 Hz), 7.9 (d, 2H, J=7.0 Hz), 7.5-7.8 (m, 5H), 7.1-7.4 (m, 7H), 5.0 (m, 1H), 4.0-4.1 (m, 1H), 4.0 (s, 3H), 3. (s, 3H), 3.6 (m, H), 2.9-3.1 (m, 4H), 2.1-2.3 (m, 2H).
M.S. Cal'd 552.1, Found 552

EXAMPLE 169
Compound **169**



H1 NMR, 300 MHz, d6 DMSO, d 9.22 (s, 2H), 9.11 (s, 2H), 7.92 (d, 2H, J=7.2 Hz), 7.80- 7.65 (m, 4H), 7.62-7.40 (m, 4H), 7.37-7.01 (m, 7H), 4.85-4.65 (m, 1H), 4.22-4.02 (m, 1H), 3.55-3.36 (m, 2H), 2.82-2.62 (m, 2H), 2.60-2.45 (m, 1H), 2.05-1.73 (m, 3H).
MS LRFAB: calc. 509, found 510 (M+H).

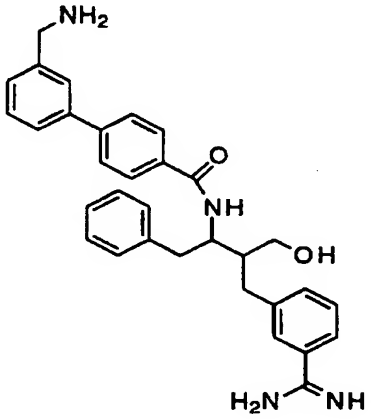
EXAMPLE 170
Compound **170**



NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=9.0 Hz), 7.7 (d, 2H, J=9.0 Hz), 7.1-7.6 (m, 11H), 4.5 (m, 1H), 4.4 (s, 2H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd, 1H,(J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.0 (d, 1H, J=7.0 Hz).
Mass spec M+H calc 549.2, found 549.

EXAMPLE 171

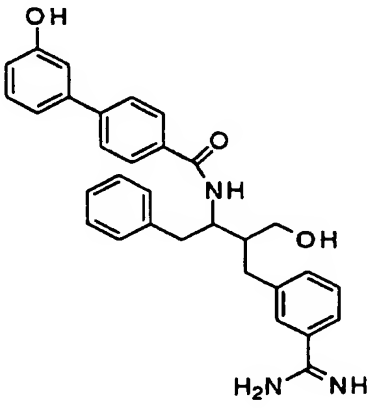
Compound **171**



NMR: 8.5 (d, 1H, J=9.0 Hz), 7.75-7.9 (m, 6H), 7.4-7.7 (m, 6H), 7.0-7.2 (m, 5H), 4.4(m, 1H), 4.2 (s, 2H), 4.0 (dd, 1H, (J=6.0 Hz,10.0 Hz), 3.7 (dd,1H, J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 1H, (J=9.0 Hz), 2.0 (m, 1H).
Mass spec M+H calc 507.3, found 507.

EXAMPLE 172

Compound **172**

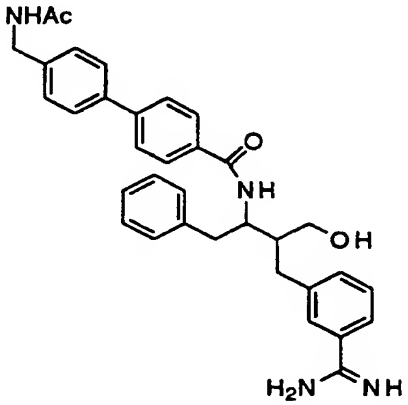


NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=10.0 Hz), 7.7 (d, 2H, J=10.0 Hz), 7.6 (d, 1H, J=10.0 Hz), 7.5 (m, 3H), 7.0-7.3 (m, 8H), 6.8 (d, 1H, J=9.0 Hz), 4.5 (m, 3H), 4.1 (dd, 1H J=6.0 Hz, 10.0 Hz), 3.9 (dd, H J=6.0 Hz, 10.0 Hz), 3.1 (d, 2H,J=9.0 Hz) 2.9 (d, 2H,J=9.0 Hz), 2.0 (m, 1H).

Mass Spec M+H calc 494.2, found 494.

EXAMPLE 173

Compound **173**

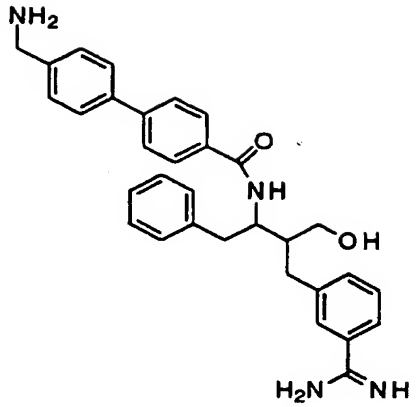


NMR: 8.5 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=10.0 Hz), 7.8 (d, 2H, J=10.0 Hz), 7.7 (d, 2H, J=10.0 Hz), 7.6 (d, 2H, J=10.0 Hz), 7.4 (s, 1H), 7.0-7.2 (m, 3H), 4.5 (m, 3H), 4.1 (dd, H J=6.0 Hz,10.0 Hz), 3.9 (dd, 1H J=6.0 Hz,10.0 Hz), 3.1 (d, 2H, J=9.0 Hz) 2.9 (d, 2H,J=9.0 Hz), 2.1 (d, 3H, J=10.0 Hz).

Mass Spec M+H calc 549.3, found 549.

EXAMPLE 174

Compound **174**

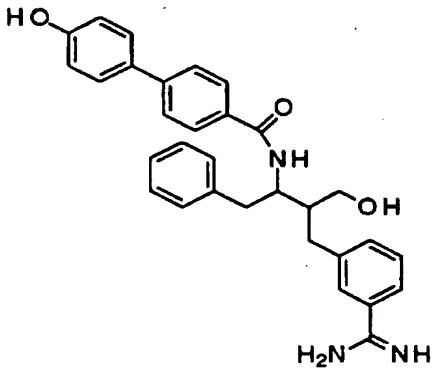


NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=8.0 Hz), 7.6-7.8 (m,4H), 7.4-7.6 (m, 4H), 7.1 7.3 (m, 4H), 6.8 (d, 2H, J=9.0 Hz), 4.3 (m, 1H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd 1H, J=6.0 Hz, 10.0 Hz), 3.0 (d, 2H, J=4.0 Hz), 2.9 (d, 1H, J=9.0 Hz), 2.0 (m, 1H)

Mass spec. M+H calc 507.3, found 507

EXAMPLE 175

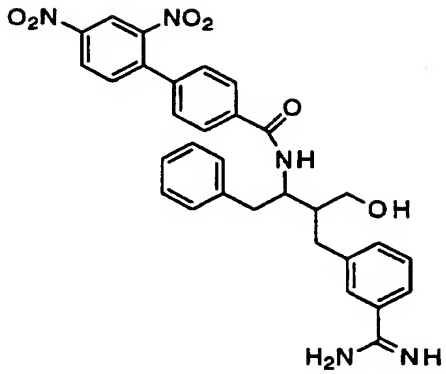
Compound **175**



M.S. Cal'd 494.2, Found 494

EXAMPLE 176

Compound **176**

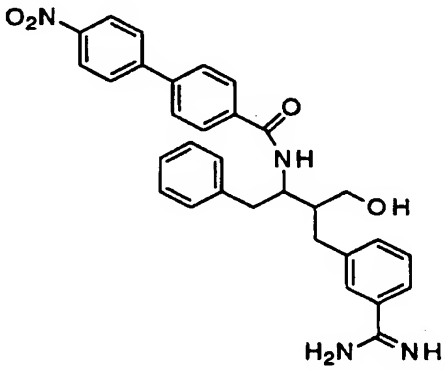


NMR 300 MHz, d6 DMSO d 9.23 (s, 2H), 9.04 (s, 2H), 8.57 (d, 1H, 9.6 Hz), 8.42 (s, 1H), 8.32 (d, 2H, 7.2 Hz), 8.13 (dd, 1H, J=1.2, 7.2 Hz), 7.75-7.40 (m, 7H), 7.25-7.13 (m, 4H), 7.12-7.05 (m, 2H), 4.48-4.35 (m, 1H), 3.58-3.42 (m, 2H), 3.10-2.62 (m, 4H), 2.15-1.95 (m, 1H).

MS (LRFAB): calc. 567, found 568 (M+H)+.

EXAMPLE 177

Compound **177**

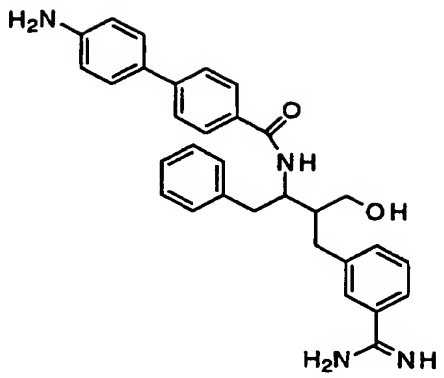


NMR 300 MHz, d6 DMSO d 9.23 (s, 2H), 8.98 (s, 2H), 8.37-8.22 (m,3H), 7.97 (d, 2H, J=7.2 Hz), 7.86 (s, 4H), 7.65-7.40 (m, 4H), 7.25-7.15 (m, 3H), 7.13-7.05 (m, 2H), 4.45-4.25 (m, 1H), 3.62-3.48 (m, 2H), 3.00-2.86 (m, 2H), 2.85-2.65 (m, 2H), 2.06-1.92 (m,1H).

MS (LRFAB): calc. 522, found 523 (M+H)+.

EXAMPLE 178

Compound **178**

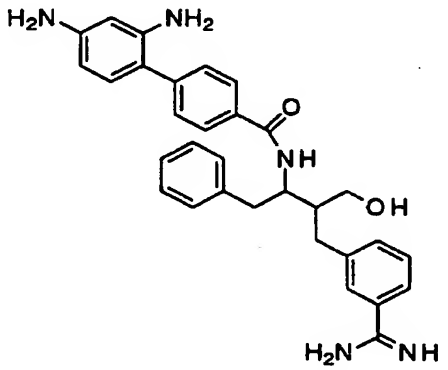


Nmr 300 MHz, d6 DMSO,9.23(d,4H,J=6 Hz), 8.28(d,1H,J=10 Hz),7.77(d,2H,J=10 Hz), 7.71-7.42(m,8H),7.22-7.12(m,4H), 7.10-7.01(m,3H), 4.45-4.25(m,1H), 3.65-3.45(m,2H), 3.05-2.87(m,2H), 2.85-2.65(m,2H), 2.05-1.95(m,1H).

MS (LRFAB): calc'd 492, found 493 (M+H)+.

EXAMPLE 179

Compound **179**

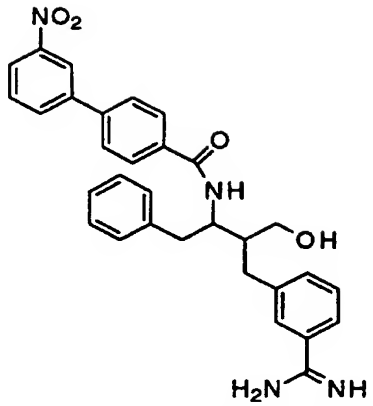


Nmr 300 MHz, d6 DMSO, 9.38-9.21(m,4H), 8.28(d,1H,J=10 Hz), 8.16(d,1H,J=10 Hz), 7.70-7.45(m,5H), 7.42(d,2H,J=7 Hz), 7.23(s,1H), 7.21-7.03(m,8H), 4.48-4.23(m,1H), 3.64-3.40(m,2H), 3.10-2.85(m,2H), 2.84-2.62(m,2H), 2.03-1.87(m,1H).

MS (LRFAB): calc'd 507, found 508 (M+H)+.

EXAMPLE 180

Compound **180**

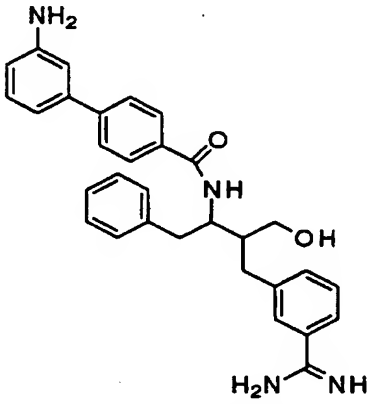


NMR 300 MHz, d6 DMSO, 9.23 (s, 2H), 8.95 (s, 2H), 8.45 (s, 1H), 8.32 (d, 1H, J=8.4 Hz), 8.24 (d, 1H, J=8.4 Hz), 8.18 (d, 1H, J=7.2 Hz), 7.86 (br.s, 4H), 7.83-7.73 (m, 1H), 7.63-7.43 (m, 4H), 7.25-7.16 (m , 4H), 7.14-7.05 (m, 1H), 4.45-4.30 (m, 1H), 3.63-3.48 (m, 2H), 3.02-2.88 (m, 2H), 2.87-2.65 (m, 2H), 2.08-1.93 (m, 1H).

MS(LRFAB): calc'd 522, found 523 (M+H)+.

EXAMPLE 181

Compound **181**

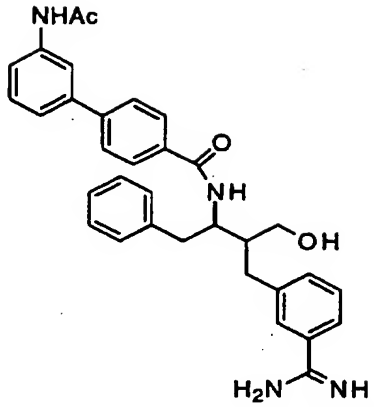


NMR 300 MHz, d6 DMSO, 9.25 (s, 2H), 9.19 (s, 2H), 8.30 (d, 1H, J=9.6 Hz), 7.82 (s, 1H), 7.82 (d, 2H ,J=7.2 Hz), 7.66 (d, 2H, J=7.2 Hz), 7.63-7.45 (m, 4H), 7.38-7.27 (m, 1H), 7.25-7.13 (m , 6H), 7.13-7.05 (m, 1H), 6.93 (d, 1H, J=8.4 Hz), 4.43-4.28 (m, 1H), 3.65-3.45 (m, 2H), 3.05-2.86 (m, 2H), 2.83-2.68 (m, 2H), 2.08-1.92 (m, 1H).

MS(LRFAB): calc'd 492, found 493 (M+H)+.

EXAMPLE 182

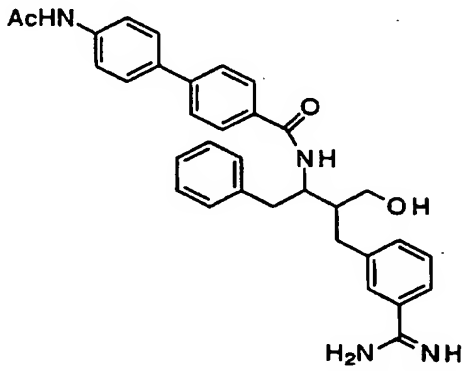
Compound **182**



Nmr 300 MHz, d6 DMSO, 9.22(s,2H), 9.07(s,2H), 8.38(d,1H,J=10 Hz), 7.93(s,1H), 7.83(d,2H,J=7 Hz), 7.65(d,2H,J=7 Hz), 7.62-7.45(m,5H), 7.42-7.28(m,2H), 7.25-7.16(m,4H), 7.13-7.07(m,1H), 4.45-4.28(m,1H), 3.63-3.53(m,2H), 3.05-2.87(m,2H), 2.85-2.68(m,2H), 2.03(s,3H), 2.02-1.93(m,1H).
MS(LRFAB): calc'd 534, found 535 (M+H)+.

EXAMPLE 183

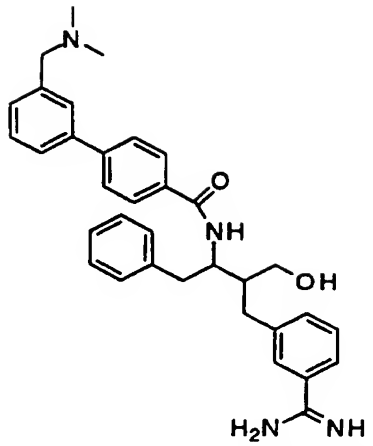
Compound **183**



Nmr 300 MHz, d6 DMSO, 10.05(s,1H),9.23(s,2H), 9.10(s,2H), 8.25(d,1H,J=10 Hz), 7.78(d,2H,J=7 Hz),7.73-7.40(m,10H), 7.21-7.13(m,4H), 7.13-7.05(m,1H), 4.43-4.25(m,1H), 3.63-3.45(m,2H), 3.03-2.85(m,2H), 2.83-2.68(m,2H), 2.04(s,3H), 2.01-1.93(m,1H).
MS(LRFAB): calc'd 534, found 535 (M+H)+.

EXAMPLE 184

Compound **184**

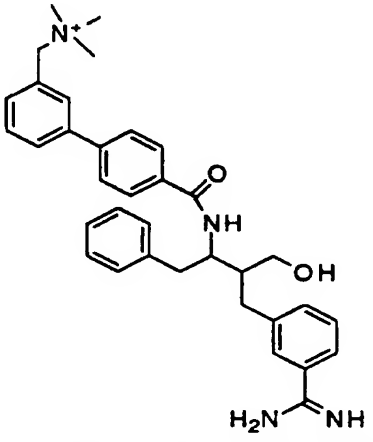


NMR: 8.5 (d, 1H, J=7.0 Hz), 7.8-8.0 (m, 6H), 7.4-7.7 (M, 6H), 7.1-7.3 (m, 5H) 4.6 (m, 3H),4.1 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.9 (s, 6H), 2.0 (m, 1H).

Mass Spec M+H calc 535.3, found 535.

EXAMPLE 185

Compound **185**

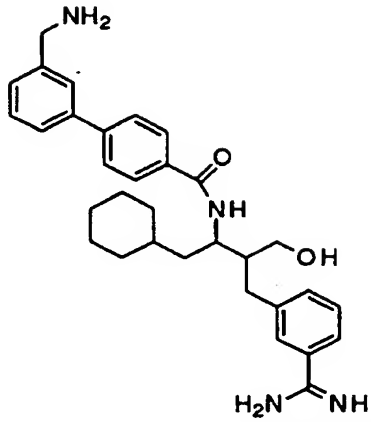


NMR: 8.5 (d, 1H, J=7.0 Hz), 7.8-8.0 (m, 6H), 7.4-7.7 (M, 6H), 7.1-7.3 (m,5H) 4.6 (m,3H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.6 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.2 (s, 9H), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.0 (m, 1H).

Mass Spec M+H calc 549.3, found 549.

EXAMPLE 186

Compound **186**

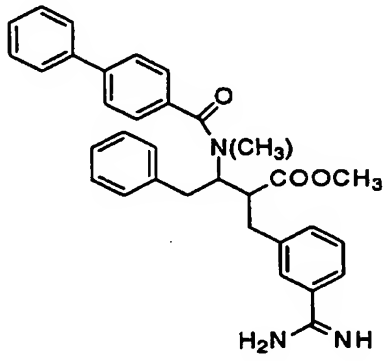


1H NMR (300 MHz, d6 DMSO), d 9.30-9.11 (m, 3H), 8.31 (br.s, 2H), 8.15 (d, 1H, J=8.4 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.86-7.68 (m, 2H), 7.64-7.48 (m, 6H), 4.30-4.15 (m,1H), 4.14-4.04 (m, 2H), 2.75 (d, 2H, J=6.0 Hz), 1.95-1.82 (m, 1H), 1.80-1.68 (m, 2H), 1.65-1.46 (m, 5H), 1.42-1.32 (m, 1H), 1.31-1.15(m, 1H), 1.13-0.93 (m, 2H), 0.92-0.65 (m, 4H).

MS, LRFAB, calc'd. 512, found 513 (M+H)+.

EXAMPLE 187

Compound **187**

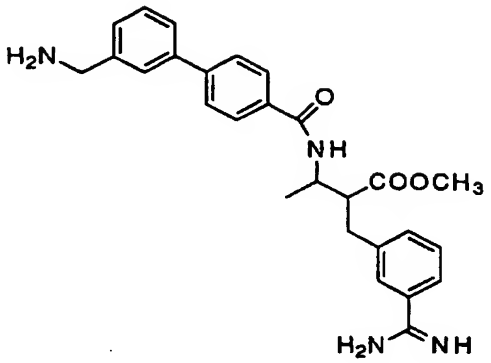


NMR: 9.0 (s, 1H), 8.5 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=9.0 Hz), 7.6-7.8 (m, 4H), 7.3-7.5 (m, 6H), 7.2-7.1 (m, 6H), 3.5 (s, 3H), 3.1 (s, 3H), 3.0 (d, 2H, J=8.0 Hz), 2.9 (d, 2H, J=8.0 Hz).

M.S. Cal'd 520.1, Found 520.

EXAMPLE 188

Compound **188**

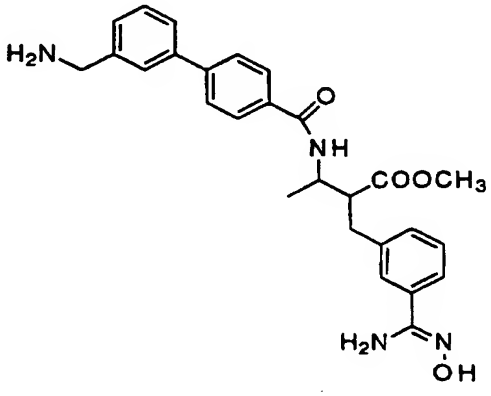


NMR: 9.4 (d, 1H, J=12.0 Hz), 8.6 (d, 1H, J=10.0 Hz), 8.1 (d, 2H, J=10.0 Hz), 7.9-8.1 (m, 4H), 7.6-7.8 (m, 6H), 4.7 (m, 1H) 4,4 (d, 2H, J=9.0 Hz), 3.7 (s, 3H), 3.1-3.4 (m, 4H), 1.6 (d, 3H,J=9.0 Hz).

Mass Spec M+H calc 459.2 found 459.

EXAMPLE 189

Compound **189**

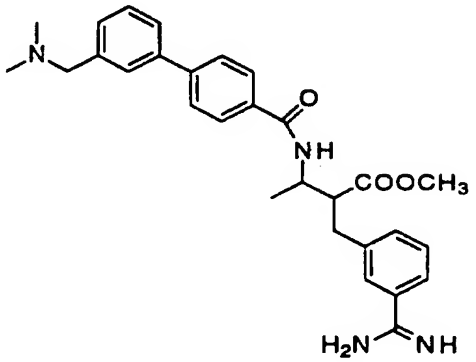


NMR: 9.4 (d, 1H, J=12.0 Hz), 8.0 (d, 1H, J=10.0 Hz), 8.1 (d, 2H, J=10.0 Hz), 7.7-7.9 (m,4H), 7.4-7.6 (m, 6H), 4.5 (m, 1H), 4.2 (d,2H, J=9.0 Hz), 3.6 (s, 3H), 3.0-3.2 (m, 3H), 1.6 (d, 3H,J=9.0 Hz).

Mass Spec M+H calc 475.1, found 475.

EXAMPLE 190

Compound **190**

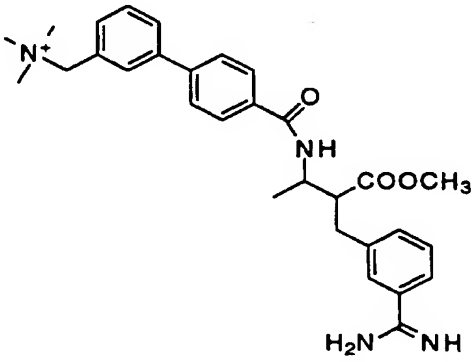


NMR: 8.4 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=10.0 Hz), 7.7-7.9 (m,4H), 7.4-7.6 (m, 6H), 4. (m,H), 4.5 (s,2H), 3.6 (s, 3H), 3.1-3.2 (m, 3H), 2.9 (s,6H), 1.3 (d, 3H,J=9.0 Hz).

Mass Spec M+H calc 459.2 found 459.

EXAMPLE 191

Compound **191**

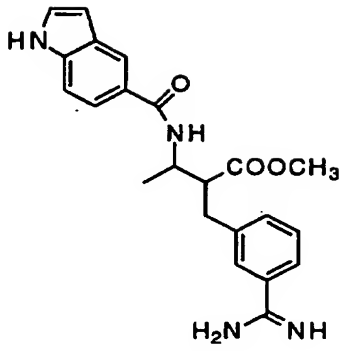


NMR: 9.3 (d, 1H, J=9.0 Hz), 9.1 (d, 1H, J=9.0 Hz), 8.4 (d, 1H, J=10.0 Hz), 7.7-8.0 (m,4H), 7.3-7.6 (m, 5H), 4.6 (s, 2H), 4,4 (m, 1H), 3.5 (s, 3H), 3.1 (s,9H), 2.9-3.1 (m, 3H) 1.6 (d, 3H,J=9.0 Hz).

Mass Spec M+H calc 501.1 found 501.

EXAMPLE 192

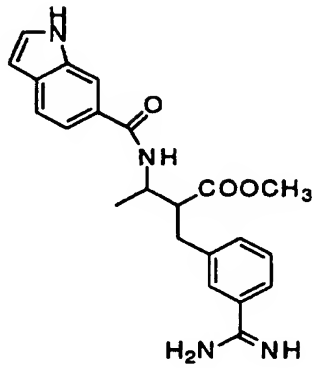
Compound **192**



M.S., APCI Cal'd 392, Found 393 $(M+H)^+$.

EXAMPLE 193

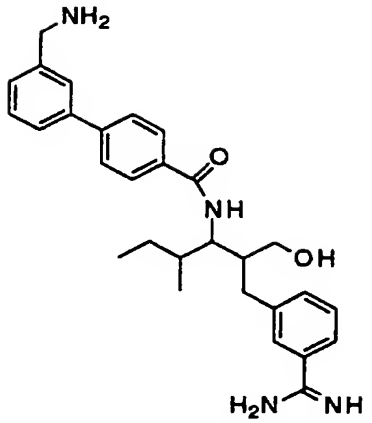
Compound **193**



M.S., APCI Cal'd 392, Found 393 $(M+H)^+$.

EXAMPLE 194

Compound **194**

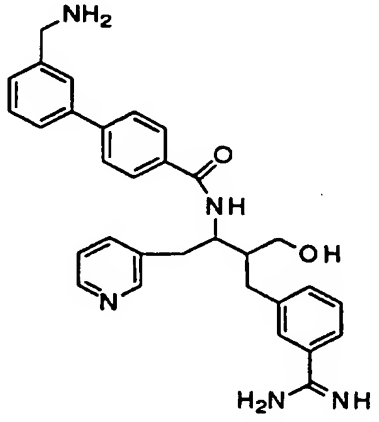


NMR: 9.4 (d, 1H, J=12.0 Hz), 8.6 (d, 1H, J=10.0 Hz), 8.0 (d, 2H, J=9.0 Hz), 7.7 (d, 2H, J=9.0 Hz) , 7.3-7.6 (m, 6H), 7.0-7.2 (m,2H), 4.2 (m,3H), 4.0 (dd, 1H, (J=6.0 Hz, 10.0 Hz), 3.6 (dd, 1H, (J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=8.0 Hz), 2.0 (m, 1H), 1.6 (m,H) 1.1-1.3 (m, 8H).

Mass Spec M+H calc 473.1, found 473.

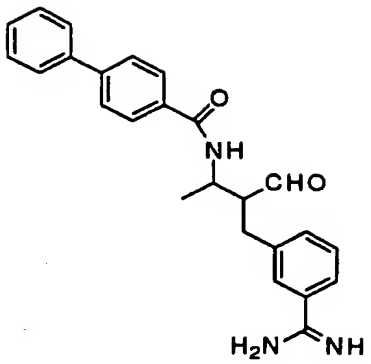
EXAMPLE 195

Compound **195**



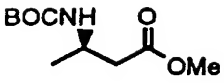
EXAMPLE 196

Compound **196**



EXAMPLE 197

Compound **197**

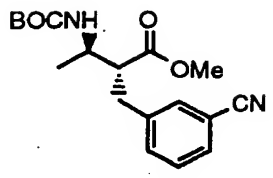


To a stirred solution of the acetic acid salt of (R)-3-aminobutyric acid methyl ester (8.9g; 50 mmol) and triethylamine (Et_3N) (21 mL; 150 mmol) in dry methylene chloride (CH_2Cl_2) under N_2 at room temperature is added di-tert-butyl dicarbonate (BOC_2O) (21.8g; 100 mmol) dropwise. 4-Dimethylaminopyridine (DMAP) (ca. 50 mg) is then added and the mixture is allowed to stir at room temperature overnight. At this point, the mixture is washed with saturated sodium bicarbonate ($NaHCO_3$) solution. The organic layer is dried over sodium sulfate (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 20% - 40% ethyl acetate (EtAc, or EtOAc) in hexanes) to give Compound **197**.

^1H NMR ($CDCl_3$, d): 4.92 (bs, 1H), 3.96 (bm, 1H), 3.65 (s, 3H), 2.45 - 2.37 (m, 2H), 1.39 (s, 9H), 1.16 (d, J = 7.9 Hz, 3H).

EXAMPLE 198

Compound **198**

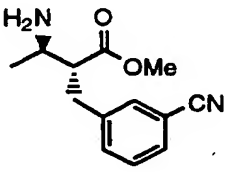


To a stirred solution of Compound **197** (2.00 g; 9.21 mmol) in 50 mL of dry tetrahydrofuran (THF) under nitrogen at -78°C is added lithium hexamethyldisilazane (LHMDS) solution (25.8 mL of 1.0 M solution in THF) dropwise. The mixture is then warmed up to -20 to -25°C for 30 min and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (4.51 g; 23.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to warm to room temperature.. After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed in vacuo. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 25% ethyl acetate / Hexanes). The semi-solid residue is then triturated with 20% EtAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to give Compound **198**.

^1H NMR ($CDCl_3$, d): 7.25 - 7.50 (m, 4H), 5.21 (bd, 1H), 3.88 (m, 1H), 3.60 (s, 3H), 3.07 - 2.73 (m, 3H), 1.48 (s, 9H), 1.14 (d, J = 7.9 Hz, 3H).

EXAMPLE 199

Compound **199**



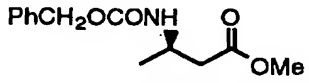
To a stirred solution of Compound **198** (4.20g; 12.7 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature is added 20 mL of trifluoroacetic acid. The

mixture is allowed to stir overnight at room temperatur and then concentrated *in vacuo* to give 4.20g of Compound **199** as the trifluoroacetic acid (TFA) salt. ^{1}H NMR (DMSO-d_6, d): 8.07 (bs, 1H), 7.73 - 7.43 (M, 4H), 3.50 (S, 3H), 3.51 (M, 1H), 3.05 - 2.82 (M, 3H), 1.23 (D, J = 7.9 HZ, 3H).

Alternatively, compound **4** may be prepared as outlined below:

EXAMPLE 200

Compound **200**

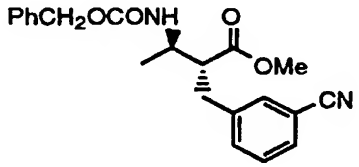


To a stirred solution of D-3-aminobutyric acid methyl ester (6.98 g; 39.4 mmol) acetic acid salt in 40 mL of CH_2Cl_2 is added sat. $NaHCO_3$ solution (40 mL). Benzyl chloroformate (9.0 mL; 63 mmol) is then added dropwise and the mixture allowed to stir vigorously at room temperature. After 3 hours, the organic layer is separated and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 10% EtAc / $CHCl_3$) to give Compound **200**.

^{1}H NMR ($CDCl_3$, d): 7.40 - 7.22 (m, 5H), 5.25 (m, 1H), 5.08 (s, 2H), 4.11 (m, 1H), 3.65 (s, 3H), 2.53 (d, J = 7.0 Hz, 2H), 1.23 (d, J = 7.9 Hz, 3H).

EXAMPLE 201

Compound **201**



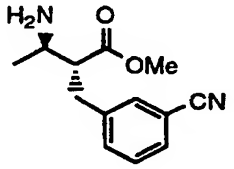
To a stirred solution of Compound **200** (3.45 g; 13.71 mmol) in 20 mL of dry THF under N_2 at -78°C is added LHMDS solution (41.2 mL of 1.0 M solution) dropwise. The mixture is then warmed up to -20°C for 30 minutes and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (4.51 g; 23.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to warm

to room temperatur . After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed in vacuo. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 30% EtAc / Hexanes). The semi-solid residue is then triturated with 20% EtAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to Compound **201**.

^1H NMR ($CDCl_3$, d) 7.20 - 7.65 (m, 9H), 5.57 (bd, 1H), 5.12 (s, 2H), 3.97 (m, 1H), 3.60 (s, 3H), 3.07 - 2.75 (m, 3H), 1.16 (d, J = 7.9 Hz, 3H).

EXAMPLE 202

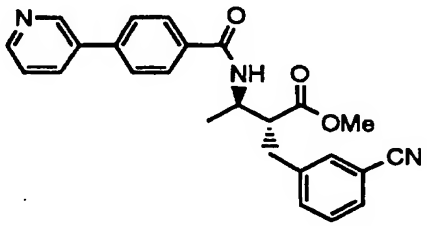
Compound **199**



To a stirred solution of Compound **201** (2.6 g; 7.1 mmol) in 25 mL of ethanol (EtOH) is added 520 mg of 10% Pd / C. The mixture is stirred under 1 atm of hydrogen for 3 hours at room temperature. The mixture is then filtered through a bed of celite to remove the catalyst. The filtrate is then concentrated in vacuo to give 1.45 g of Compound **201**.

EXAMPLE 203

Compound **203**



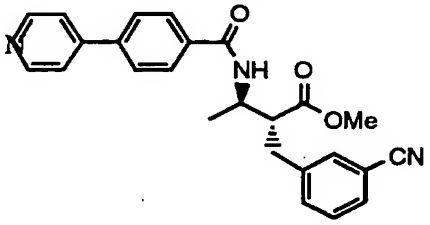
3'-pyridyl-4-phenyl carbonyl chloride (Compound **228**, prepared as in Example 228) (384 mg; 1.8 mmol) is added in one portion to a solution of Compound **199** TFA salt (373 mg; 1.6 mmol) and Et_3N (0.67 mL; 4.8 mmol) in

5.0 mL of absolute EtOH under N_2 at room temperature. The mixture is allow d to stir overnight at room temperature. The solvent is then removed *in vacuo* and the crude product is purified by chromatography on silica gel (eluent = 70% EtAc / Hexanes) to provide Compound **203**.

^{1}H NMR ($CDCl_3$, d): 8.88 (m, 1H), 8.63 (m, 1H), 7.85 - 8.00 (m, 7.70 (m, 2H), 7.57 - 7.33 (m, 6H), 4.51 (m, 1H), 3.65 (s, 3H), 3.10 - 2.82 (m, 3H), 1.28 (d, J = 7.9 Hz, 3H).

EXAMPLE 204

Compound **204**

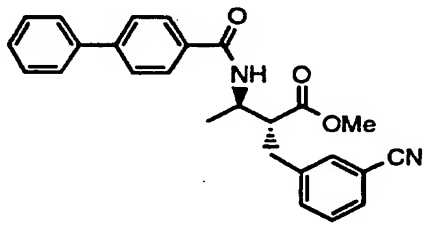


Acylation of Compound **199** according to the procedure of Example 203, substituting Compound **228** with 4'-pyridyl-4-phenylcarbonyl chloride (Compound **231**, prepared as in Example 231) provides, after workup and chromatography, Compound **204**.

^{1}H NMR ($CDCl_3$, d): 8.70 (m, 2H), 8.02 - 7.65 (m, 4H), 7.57 - 7.32 (m, 7H), 4.50 (m, 1H), 3.68 (s, 3H), 3.10 - 2.83 (M, 3H), 1.30 (d, J = 7.9 Hz, 3H).

EXAMPLE 205

Compound **205**



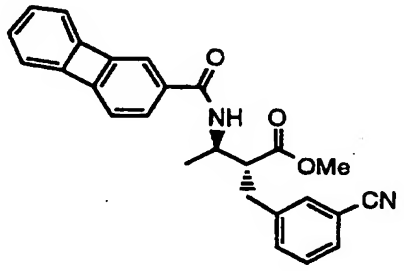
Acylation of Compound **199** according to Example 203, in CH_2Cl_2 rather than absolute EtOH, and substituting 3'-pyridyl-4-phenylcarbonyl chloride with 4-

biphenylcarbonyl chloride provides, after workup and chromatography, Compound **205**.

^{1}H NMR ($CDCl_3$, d): 7.93 (m, 2H), 7.73 - 7.30 (m, 12H), 4.50 (m, 1H), 3.66 (s, 3H), 3.10 - 2.83 (m, 3H), 1.26 (d, J = 7.9 Hz, 3H).

EXAMPLE 206

Compound **206**

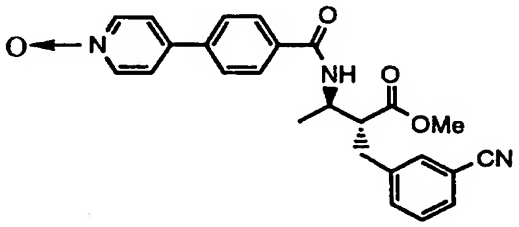


Acylation of Compound **199** according to Example 203 substituting 3'-pyridyl-4-phenylcarbonyl chloride with 2-biphenylenecarbonyl chloride provides, after workup and chromatography, Compound **206**.

^{1}H NMR ($CDCl_3$, d): 7.55 - 7.27 (m, 5H), 7.07 (m, 2H), 6.85 - 6.66 (m, 5H), 4.44 (m, 1H), 3.65 (s, 3H), 3.05 - 2.80 (m, 3H), 1.23 (d, J = 7.9 Hz, 3H).

EXAMPLE 207

Compound **207**



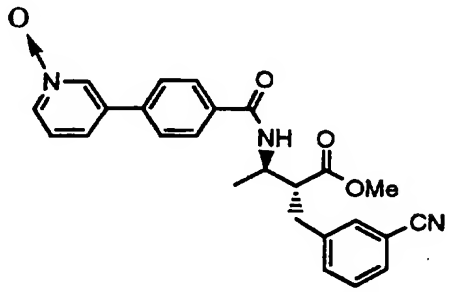
Add m-chloroperbenzoic acid (mCPBA) (381 mg; 2.21 mmol) to a solution of Compound **204** (608 mg; 1.47 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature. The resulting mixture is allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with

5% Na_2CO_3 solution. The organic layer is dried (Na_2SO_4), filt red and concentrated to give Compound **207**.

MS: $M^{+\cdot}$ + H^+ (Calc.) = 430 ; Found (FAB) = 430.

EXAMPLE 208

Compound **208**

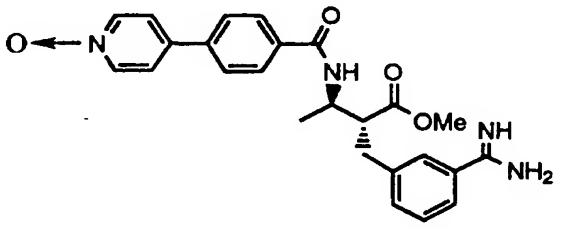


Add mCPBA (124 mg; 0.72 mmol) to a solution of Compound **203** (150 mg; 0.36 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature. The resulting mixture is allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with 5% Na_2CO_3 solution. The organic layer is dried (Na_2SO_4), filtered and concentrated to give Compound **208**.

^1H NMR ($CDCl_3$, d): 8.57 (m, 1H), 8.30 (m, 1H), 7.95 (m, 2H), 7.73 - 7.35 (m, 9H), 4.50 (m, 1H), 3.68 (s, 3H), 3.07 - 2.85 (m, 3H), 1.20 (d, J = 7.9 Hz, 3H).

EXAMPLE 209

Compound **209**



Bubble hydrogen chloride gas (HCl (g)) into a solution of Compound **207** (480 mg) in 5.0 mL of dry methanol (MeOH) containing 3Å molecular sieves (pellets,

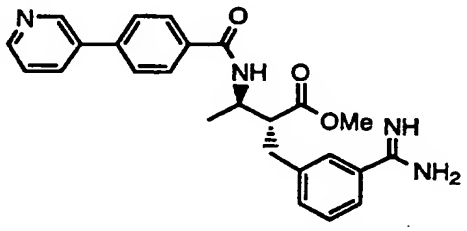
ca. 50 mg) for about 2 minutes at room temperature. The mixture is allowed to stir overnight at room temperature and then concentrated *in vacuo*. A solution of ammonia (NH_3) in MeOH (5.0 mL of 7N solution) is added and the mixture refluxed for 1 hour. The solvent is then removed *in vacuo* and the crude product purified by RPHPLC (CH_3CN / H_2O, 0.1% TFA, gradient:10% to 100% CH_3CN and the fractions containing product are lyophilized to give Compound **209**.

^1H NMR (MeOH-d_4, d): 8.42 (m, 2H), 8.00 - 7.85 (m, 6H), 7.68 - 7.47 (m, 4H), 4.47 (m, 1H), 3.60 (s, 3H), 3.18 - 3.00 (m, 3H), 1.33 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot} + H^+$ (Calc.) = 447 ; Found (FAB) = 447.

EXAMPLE 210

Compound **210**



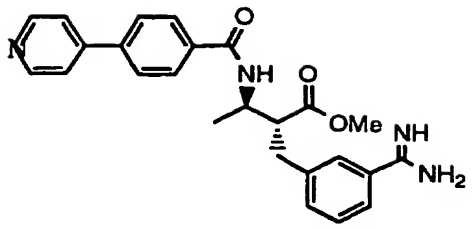
Treatment of Compound **203** in a similar manner as in Example 209 provides, after purification by RPHPLC, Compound **210**.

1H NMR (DMSO-d6, d): 9.36 (m, 3H), 8.50 - 8.27 (m, 2H), 8.00 - 7.80 (m, 3H), 7.80 - 7.40 (m, 4H), 4.40 (m, 1H), 3.49 (s, 3H), 3.13 - 2.81 (m, 3H), 1.25 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot} + H^+$ (Calc.) = 431 ; Found (FAB) = 431

EXAMPLE 211

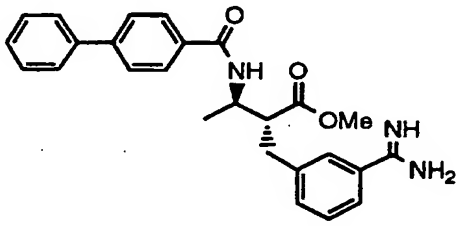
Compound **211**



Treatment of Compound **204** in a similar manner as in Example 209 provides, after purification by RPHPLC, Compound **211**.

EXAMPLE 216

Compound **216**



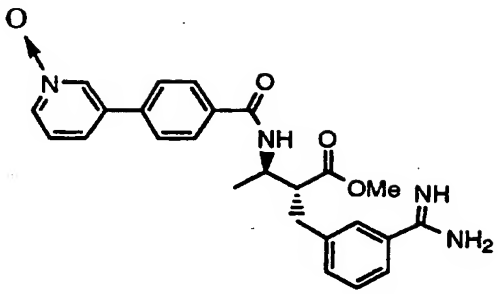
Treatment of Compound **205** in a similar manner as in Example 209 above provides, after purification by RPHPLC, compound **216**.

^{1}H NMR (DMSO-d_6, d): 9.30 (s, 1H), 9.00 (s, 1H), 8.40 (m, 1H), 8.05 - 7.40 (m, 12 H), 4.46 (m, 1H), 3.56 (s, 3H), 3.20 -2.97 (m, 3H), 1.28 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot} + H^+$ (Calc.) = 430 ; Found (FAB) = 430.

EXAMPLE 217

Compound **217**



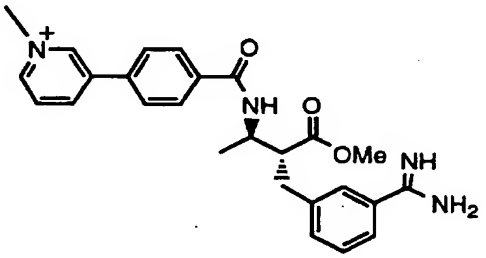
Treatment of Compound **208** in a similar manner as in Example 209 above provides, after purification by RPHPLC, Compound **217**.

^{1}H NMR (MeOH-d_4, d): 8.67 (m, 1H), 8.50 - 8.35 (m, 2H), 8.00 - 7.78 (m, 5H), 7.72 - 7.48 (m, 5H), 4.47 (m, 1H), 3.60 (s, 3H), 3.16 - 3.05 (m, 3H), 1.32 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot} + H^+$ (Calc.) = 447 ; Found (FAB) = 447.

EXAMPLE 218

Compound **218**



Hydrogen sulfide gas (H_2S) is bubbled into a solution of Compound **203** (498 mg; 1.21 mmol) in 5.0 mL of pyridine and 1.0 mL of Et_3N for ca. 2 minutes. The resulting mixture is allowed to stir overnight at room temperature and then concentrated to dryness under a stream of N_2. The residue is taken up into 5 mL of CH_2Cl_2 and 5 mL of methyl iodide is added. The mixture is refluxed for 3 hours, allowed to cool to room temperature and concentrated *in vacuo*. The residue is then taken up into 5 mL dry MeOH and NH_4OAc (300 mg) is added. The resulting mixture is refluxed for 3h and then concentrated *in vacuo*. The crude product is purified by RPHPLC (CH_3CN / H_2O, 0.1% TFA, gradient:10%

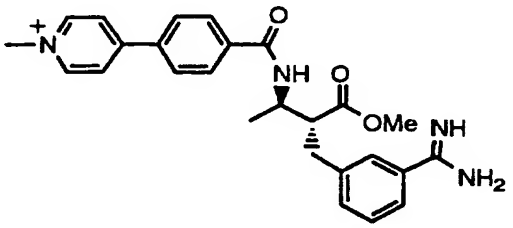
to 100% CH_3CN and the fractions containing product are lyophilized to give Compound **218**.

^1H NMR (MeOH-d_4, d): 9.35 (s, 1H), 8.92 (m, 2H), 8.50 (d, 1H), 8.17 (m, 1H), 8.08 - 7.92 (m, 4H), 7.66 - 7.50 (m, 4H), 4.50 (s, 3H), 4.50 (m, 1H), 3.58 (s, 3H), 3.15 - 3.02 (m, 3H), 1.34 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot}$ (Calc.) = 445 ; Found (FAB) = 445.

EXAMPLE 219

Compound **219**



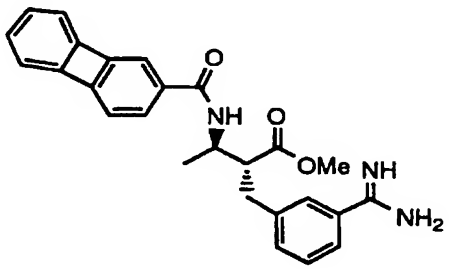
Treatment of Compound **204** in a similar manner to that of Compound **203** in EXAMPLE 218 above provides, after purification by RPHPLC, Compound **219**.

^1H NMR (DMSO-d_6, d): 9.05 (m, 1H), 8.55 (m, 3H), 8.20 - 7.97 (m, 5H), 7.65 - 7.47 (m, 4H), 4.33 (s, 3H), 4.10 (m, 1H), 3.13 (s, 3H), 3.13 - 2.90 (m, 3H), 1.27 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot}$ (Calc.) = 445 ; Found (FAB) = 445.

EXAMPLE 220

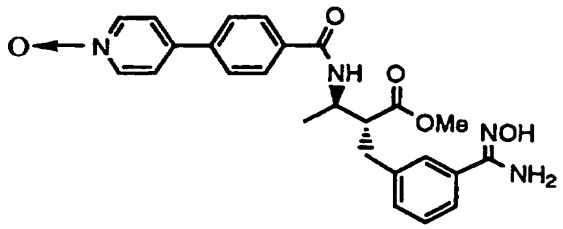
Compound **220**



Treatment of Compound **206** in a similar manner to that of Compound **203** in EXAMPLE 218 above provides, after purification by RPHPLC, compound **220**.

EXAMPLE 221

Compound **221**



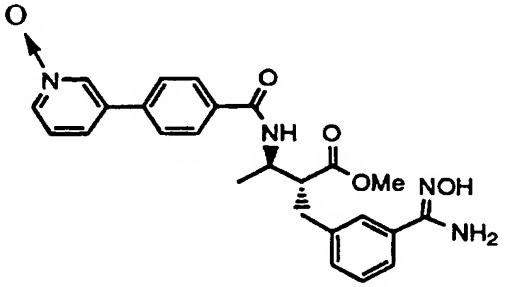
To a stirred solution of sodium methoxide in MeOH (12.4 mL of 0.5 M solution) is added hydroxylamine hydrochloride. Once all the solid dissolves, the solution is added to a solution of Compound **207** (530 mg; 1.24 mmol) in 5 mL of MeOH at room temperature. The resulting mixture is allowed to stir at room temperature under N_2 overnight. At this point, the solvent is removed *in vacuo* and the product purified by flash chromatography (eluent = 10% MeOH / CH_2Cl_2). The fractions containing product are concentrated *in vacuo* and the residue is then lyophilized from water to give Compound **221.**

^1H NMR ($CDCl_3$, d): 9.60 (s, 1H), 8.60 - 7.10 (m, 12H), 5.80 (bs, 1H), 4.40 (m, 1H), 4.45 (s, 3H), 3.15 - 2.80 (m, 3H), 1.15 (d, J = 7.9 Hz, 3H).

MS: $M^{+\cdot} + H^+$ (Calc.) = 463 ; Found (FAB) = 463.

EXAMPLE 222

Compound **222**



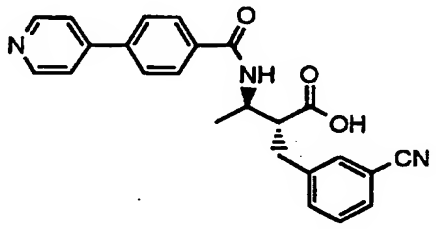
Treatment of Compound **208** in a similar manner to that of Compound **207** in Example 221 above provides, after purification by flash chromatography, compound **222**.

^{1}H NMR (MeOH-d_4, d): 8.69 (m, 1H), 8.35 (m, 1H), 8.00 - 7.75 (m, 5H), 7.72 - 7.25 (m, 5H), 4.47 (m, 1H), 3.57 9s, 3H), 3.15 - 2.95 (m, 3H), 1.33 (d, J =- 7.9 Hz, 3H).

MS: $M^{+\cdot}$ + H^+(Calc.) = 463 ; Found (ion spray) = 463.

EXAMPLE 223

Compound **223**

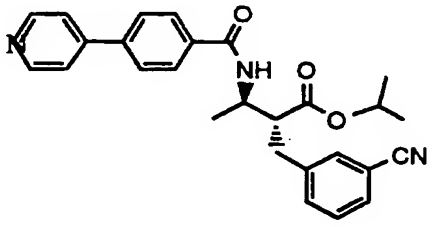


To a stirred solution of Compound **204** (319 mg; 0.77 mmol) in 4 mL of MeOH / THF (1 / 1) is added 1 N NaOH solution (10 mL). The resulting mixture is allowed to stir for 2 hours at room temperature and then acidified with 12 mL of 1 N HCl solution. The solid product Compound **223** is filtered off and dried *in vacuo*.

^{1}H NMR ($CDCl_3$, d): 9.30 (bs, 1H), 8.50 (bs, 1H), 8.30 - 7.80 (m, 6H), 7.65 - 7.28 (m, 5H), 4.40 (m, 1H), 3.20 - 2.85 (m, 3H), a.33 (d, J = 7.9 Hz, 3H).

EXAMPLE 224

Compound **224**

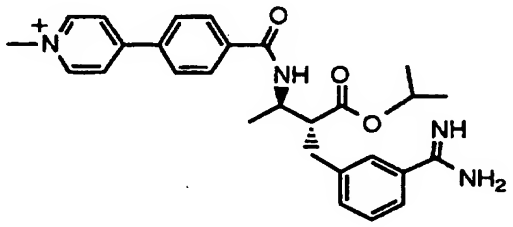


Triethylamine (0.11 mL; 0.77 mmol) is added dropwise to a suspension of Compound **223** in dry CH_2Cl_2 (10 mL) under N_2 at room temperature. After 10 minutes, isopropyl chloroformate (0.77 mL; 0.77 mmol) is added dropwise. After 30 minutes, DMAP (31 mg) is added and the mixture allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed with 40% EtOAc / hexanes followed by 70% EtOAc / hexanes to give Compound **224**.

MS: $M^{+\cdot}$ + H+ (Calc.) = 442 ; Found (Ion spray) = 442.

EXAMPLE 225

Compound **225**



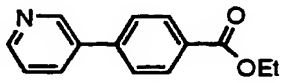
Treatment of Compound **224** in a similar manner to that of Compound **203** in Example 218 above provides, after purification by RPHPLC, Compound **225**.

^1H NMR (DMSO-d_6, d): 9.28 (m, 1H), 9.00 (m, 3H), 8.53 (m, 1H), 8.23 - 7.92 (m, 4H), 7.32 (s, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 4.38 (m, 1H), 4.32 (s, 3H), 3.14 - 2.93 (m, 3H), 1.25 (m, 3H), 0.99 (m, 3H), 0.87 (m, 3H).

MS: $M^{+\cdot}$ (Calc.) = 473 ; Found (FAB) = 473.

EXAMPLE 226

Compound **226**



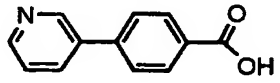
Ethyl-4-bromobenzoate (7.0g; 31 mmol) is dissolved in 100 mL of THF. To this solution is added $Pd(Ph_3P)_4$ (1.0g; 1.0 mmol), tetrabutylammonium bromide

(592 mg; 1.8 mmol), powdered potassium hydroxide (KOH) (3.4g; 61 mmol) and diethyl-(3-pyridyl)borane (3.0g). The resulting mixture is refluxed for 2.5 hours, allowed to cool to room temperature and concentrated in vacuo. The crude product is taken up into MeOH and chromatographed (eluent = gradient, 50% EtAc / Hexanes to 70% EtAc / Hexanes) to give, after solvent evaporation, Compound **226**.

^{1}H NMR ($CDCl_3$, d): 8.83 (s, 1H), 8.60 (m, 1H), 8.10 (m, 2H), 7.90 - 7.30 (m, 3H), 4.34 (m, 2H), 1.37 (m, 3H).

EXAMPLE 227

Compound **227**

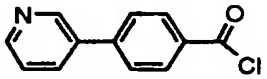


Sodium hydroxide solution (25.5 mL of 1.0N solution) is added dropwise to a stirred solution of Compound **226** (2.7g; 12 mmol) in 21 mL of 1 / 1 THF / MeOH at room temperature. After 3 hours, 25 mL of 1N HCl is added and the white precipitate is filtered off. The solid is dried *in vacuo*. to give Compound **227**.

^{1}H NMR (DMSO-d_6, d): 8.90 (s, 1H), 8.60 (s, 1H), 8.13 (m, 1H), 8.05 - 7.80 (m, 4H), 7.50 (m, 1H).

EXAMPLE 228

Compound **228**

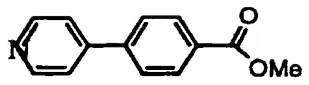


Thionyl chloride (5 mL) is added to 1.3 g of Compound **227**. The resulting mixture is refluxed for 2 hours and then concentrated *in vacuo* to give Compound **228**.

MS: $M^{+\cdot}$ (Calc.) = 217 ; Found (EI) = 217.

EXAMPLE 229

Compound **229**

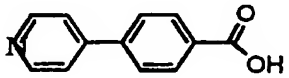


A mixture of methyl coumalate (10g; 65 mmol), 4-vinylpyridine (35 mL; 325 mmol) and 10% Pd / C (25g) in mesitylene (300 mL) is heated at 200°C for 30 hours. At this point, the mixture is allowed to cool and filtered through celite washing with $CHCl_3$. Most of the solvent is then removed *in vacuo* and the remaining liquid is chromatographed (eluent: Gradient, 50% EtAc / Hex. to 70% EtAc / Hex.) to give Compound **229**.

MS: $M^{+\cdot}$ (Calc.) = 213 ; Found (EI) = 213.

EXAMPLE 230

Compound **230**

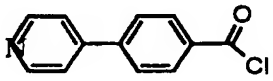


Treatment of Compound **229** with sodium hydroxide in THF / MeOH as in Example 227 provides Compound **230**.

MS: $M^{+\cdot}$ (Calc.) = 199 ; Found (EI) = 199.

EXAMPLE 231

Compound **231**

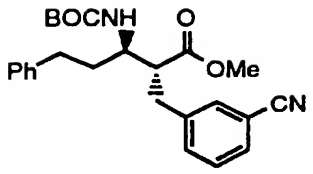


Treatment of Compound **230** with refluxing thionyl chloride as in Example 228 provides Compound **231**.

MS: $M^{+\cdot}$ (Calc.) = 217 ; Found (EI) = 217.

EXAMPLE 232

Compound **232**

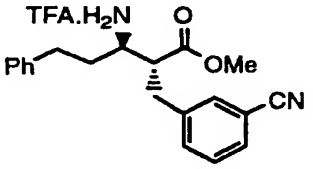


To N-BOC homophenylalanine methylester (5.57g; 18.1 mmol) in 30 mL of THF under N_2 at -78°C is added LHMDS solution dropwise (54.3 mL of 1N solution in THF). The mixture is then allowed to warm up to 0°C for 30 min and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (7.46 g; 38.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to warm to room temperature. After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed *in vacuo*. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 25% EtAc / Hexanes. The semi-solid residue is then triturated with 20% EtAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to Compound **232**

^1H NMR ($CDCl_3$, d): 7.82 - 7.08 ((m, 9H), 5.32 (bd, 1H), 3.84 (m, 1H), 3.60 (s, 3H), 3.06 - 2.57 (m, 5H), 1.70 (m, 2H), 1.47 (s, 9H).

EXAMPLE 233

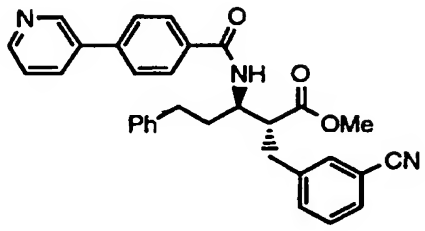
Compound **233**



To a stirred solution of Compound **232** (1.42g; 3.35 mmol) in 5.0 mL of CH_2Cl_2 under N_2 at 0°C is added 3.5 mL of trifluoroacetic acid. The mixture is allowed to stir for 2 hours at room temperature and then concentrated *in vacuo* to give Compound **233** as the TFA salt.

MS: $M^{+\cdot}$ (Calc.) = 322 ; Found (EI) = 322.

EXAMPLE 234

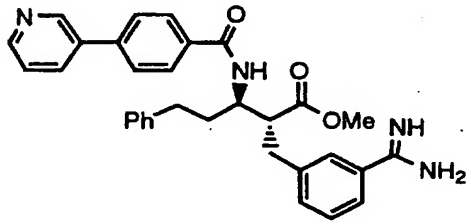


Acylation of Compound **233** according to Example 203 with Compound **228** provides, after workup and chromatography, Compound **234**.

MS: $M^{+\cdot}$ (Calc.) = 503 ; Found (EI) = 503.

EXAMPLE 235

Compound **235**

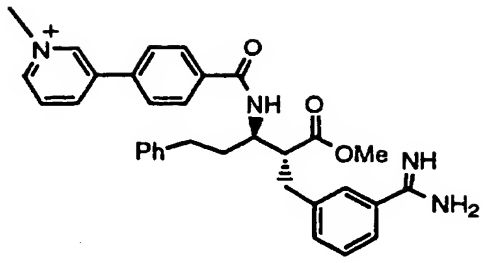


Treatment of Compound **234** with HCl / MeOH, then NH_4OAc in a similar manner to Compound **207** in Example 209 above provides, after purification by RPHPLC, Compound **235**.

MS: $M^{+\cdot}$ + H+ (Calc.) = 521 ; Found (FAB) = 521.

EXAMPLE 236

Compound **236**

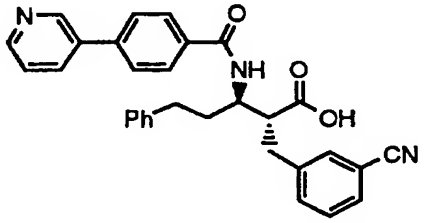


Treatment of Compound **234** in a similar manner to that of Compound **203** in EXAMPLE 218 above provides, after purification by RPHPLC, Compound **236**.

^{1}H NMR (MeOH-d$_4$): 9.35 (s, 1H), 8.90 (m, 2H), 8.45 (m, 1H), 8.17 (m, 1H), 8.11 - 7.92 (m, 4H), 7.68 - 7.46 (m, 5H), 7.27 - 7.10 (m, 6H), 4.50 (s, 3H), 4.40 (m, 1H), 3.57 (s, 3H), 3.05 (m, 3H), 2.67 (m, 2H), 2.00 (m, 2H).

EXAMPLE 237

Compound **237**

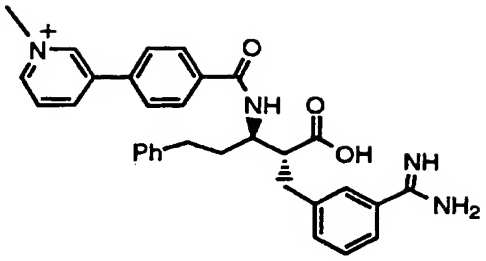


Hydrolysis of Compound **234** with sodium hydroxide in THF / MeOH using the procedure of Example 227 provides after workup, Compound **237**.

MS: $M^{+\cdot}$ + H+ (Calc.) = 490 ; Found (FAB) = 490.

EXAMPLE 238

Compound **238**



Treatment of Compound **237** in a similar manner to Compound **203** in Example 218 above provides, after purification by RPHPLC, Compound **238** ^{1}H NMR (MeOH-d4): 9.38 (s, 1H), 8.90 (m, 2H), 8.47 (m, 1H), 8.17 (m, 1H), 8.11 - 7.92 (m, 4H), 7.68 - 7.46 (m, 5H), 7.26 - 7.10 (m, 6H), 4.50 (s, 3H), 4.38 (m, 1H), 3.12 - 2.97 (m,. 3H), 2.68 (m, 2H), 2.03 (m, 2H).

The molecules described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, factor Xa, rather than thrombin. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel

luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of factor Xa inhibitors with standard heparin, low molecular weight heparin, direct thrombin inhibitors (i.e. hirudin), aspirin, fibrinogen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator may result in greater antithrombotic or thrombolytic efficacy or efficiency. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans, sheep, horses, cattle, pigs, dogs, rats and mice. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any factor Xa inhibitor can be added to or contacted with any medium containing or suspected of containing factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a pathologic role. For example, thrombin has been proposed to contribute to the morbidity and

mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor. Inhibition of factor Xa will effectively block thrombin generation and therefore neutralize any pathologic effects of thrombin on various cell types.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously intramuscularly, colonically, nasally, intraperitoneally, rectally or orally.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The perc ntage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature and below which tests results are believed to correlate to pharmacological activity in humans and other mammals.

Enzyme Assays:

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by

determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional *in vitro* assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the *in situ* generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the *ex vivo* effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this *in vitro* assay is considered as a surrogate marker for *in vivo* anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 µl of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 µl of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and

placed in the instrument. Following a 3 minut warming period the instrument automatically adds 100 µl of activated cephaloplastin reagent (Actin, Dade) followed by 100 µl of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

Compounds according to the invention may also be evaluated for their *in vivo* antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental *In Vivo* Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) *in vivo* generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 mL/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 mL/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just

proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 mL of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 mL ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental *In Vivo* Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model,

R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 mL of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow

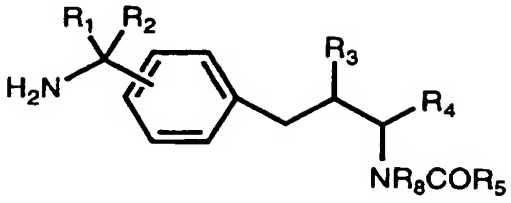
reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minut s, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 mL/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

By way of example, Compound **184** shows K_i values of 27.0 nM, 1.72 μM, and 2.71 μM, in the Factor Xa, trypsin, and thrombin assays, respectively. Compound **45** shows K_i values of 94.0 nM, 129 nM, and 477 nM, in the Factor Xa, trypsin, and thrombin assays, respectively. Compound **167** shows K_i values of 19.0 nM, 46 nM, and 1.228 μM, in the Factor Xa, trypsin, and thrombin assays, respectively.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED IS:

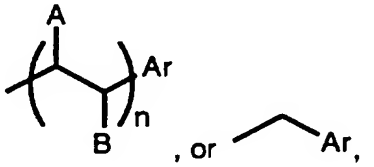
1. A compound of the formula



R_1 and R_2 are hydrogen or taken together are $=NR_9$;

R_3 is $-CO_2R_6$, $-C(O)R_6$, $-CONR_6R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

R_4 is a group of formula



or R_4 is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl;

R_5 is alkyl, alkenyl, optionally substituted aryl or optionally substituted heteroaryl;

R_6 is hydrogen or lower alkyl;

R_7 is hydrogen, lower alkyl, lower acyl, aroyl or heteroaryl;

R_8 is hydrogen or lower alkyl;

R_9 is $R_{10}O_2C$-, $R_{10}O$-, HO-, cyano, $R_{10}CO$-, HCO-, lower alkyl, nitro, or Y^1Y^2N-, where R_{10} is optionally substituted alkyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl, and where Y^1 and Y^2 are independently hydrogen or alkyl;

A and B are hydrogen or taken together are a bond;

Ar is optionally substituted aryl or optionally substituted heteroaryl; and

n is 0, 1 or 2; or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

2. The compound of claim 1 wherein R_1 and R_2 taken together are =NH.

3. The compound of claim 2 wherein R_1 and R_2 taken together are =NH and form an aminoiminomethyl on the phenyl moiety that is in the meta position to the position of attachment of the phenyl moiety to the propyl moiety.

4. The compound of claim 1 wherein R_3 is $-CO_2R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

5. The compound of claim 4 wherein R_3 is $-CO_2R_6$ and R_6 is lower alkyl.

6. The compound of claim 4 wherein R_3 is $-CH_2OR_7$ or $-CH_2SR_7$ and R_7 is hydrogen or lower alkyl.

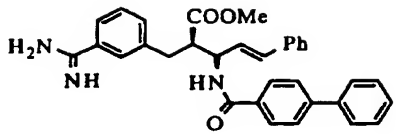
7. The compound of claim 1 wherein n is 1.

8. The compound of claim 1 wherein Ar is optionally substituted aryl.

9. The compound of claim 1 wherein Ar is phenyl.

10. The compound of claim 1 wherein R_5 is optionally substituted phenyl, optionally substituted biphenyl, optionally substituted naphthyl, or optionally substituted heterobiphenyl.

11. A compound according to claim 1 which is: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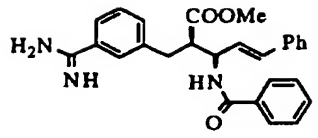
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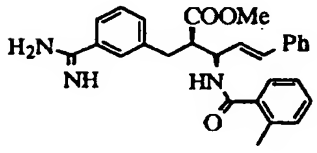
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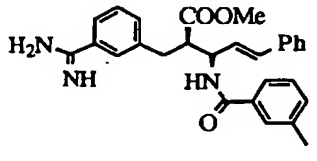
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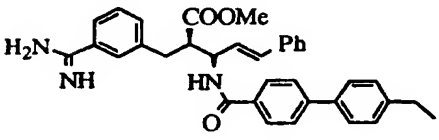
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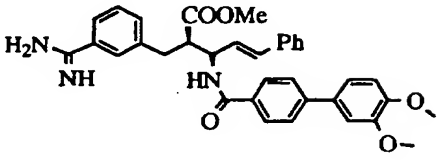
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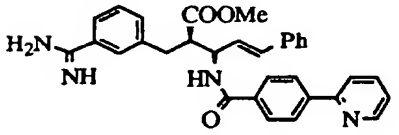
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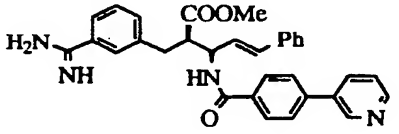
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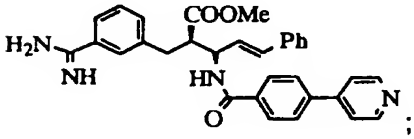
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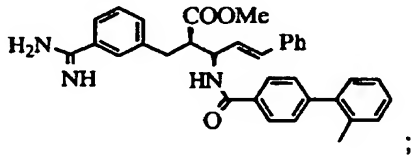
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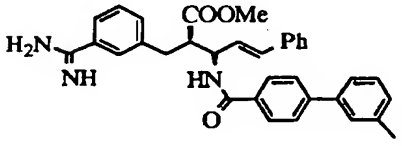
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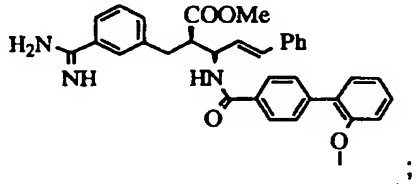
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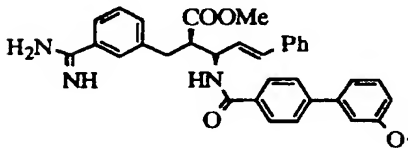
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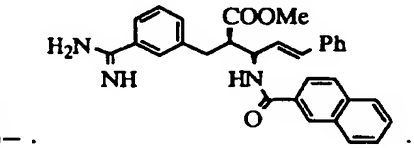
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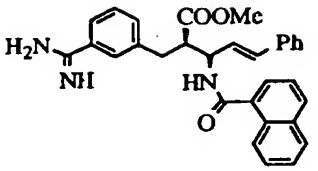
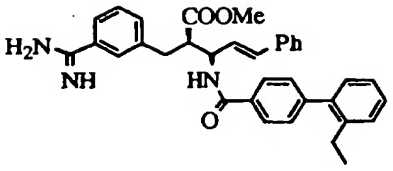
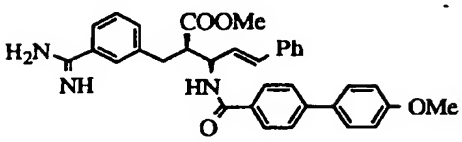
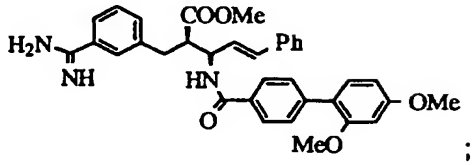
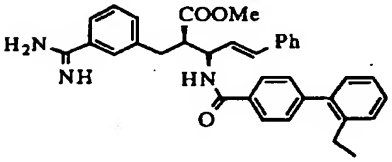
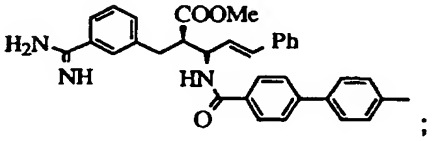
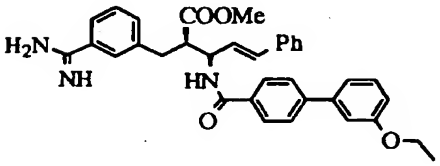
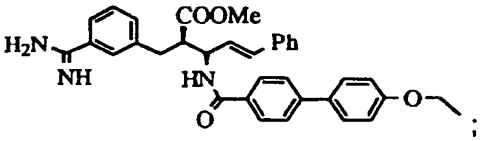
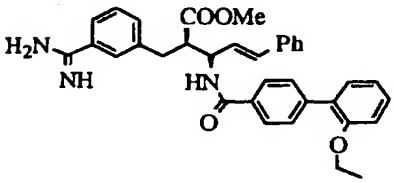
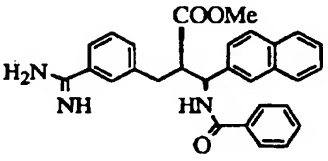
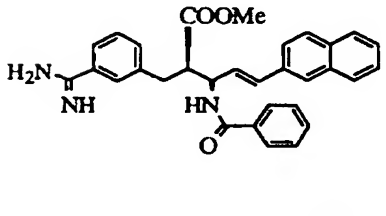
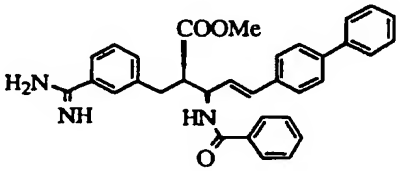
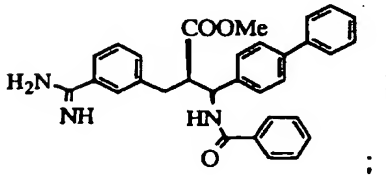
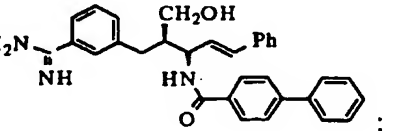

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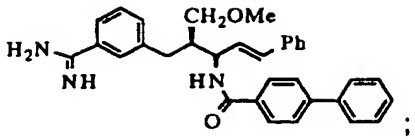
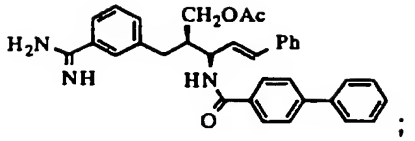
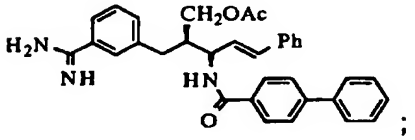
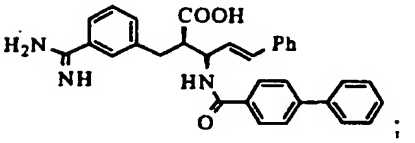
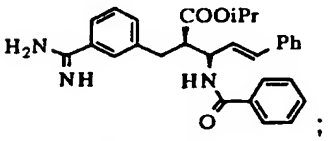

CH2OMe
Ph
H2N
NH
HN
O
;

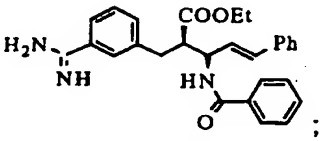

CH2OAc
Ph
H2N
NH
HN
O
;

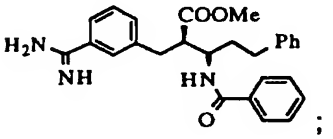

CH2OAc
Ph
H2N
NH
HN
O
;

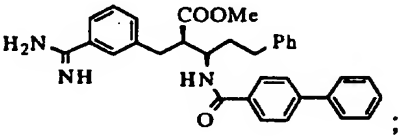

COOH
Ph
H2N
NH
HN
O
;

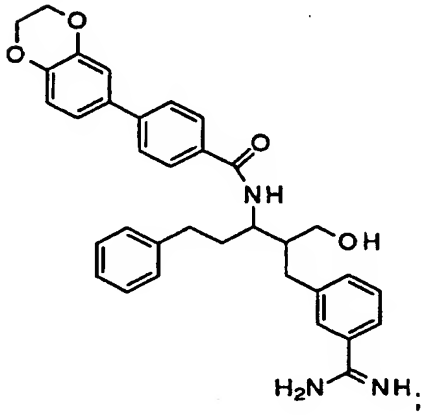
5

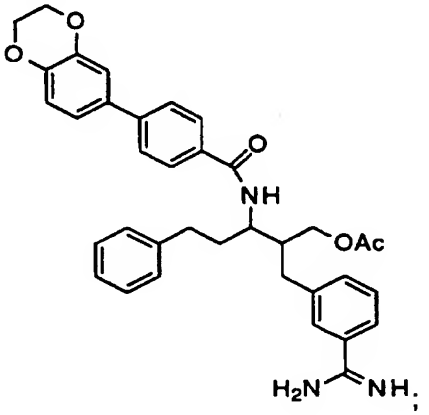

COOiPr
Ph
H2N
NH
HN
O
;


COOEt
Ph
H2N
NH
HN
O
;

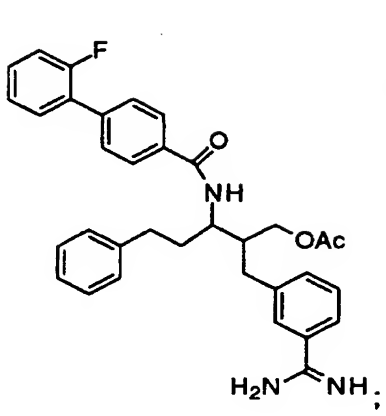

COOMe
Ph
H2N
NH
HN
O
;

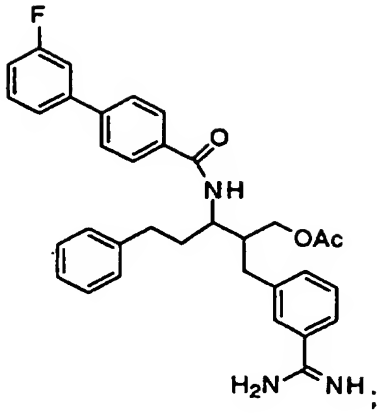

COOMe
Ph
H2N
NH
HN
O
;

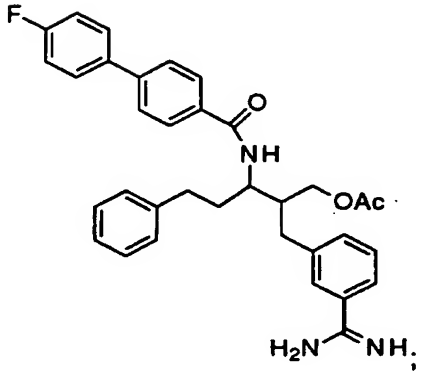

O
O
O
NH
OH
H2N
NH
;

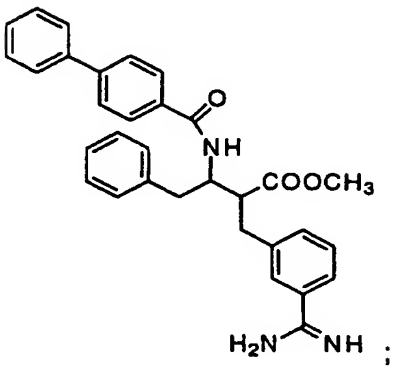

O
O
O
NH
OAc
H2N
NH
;

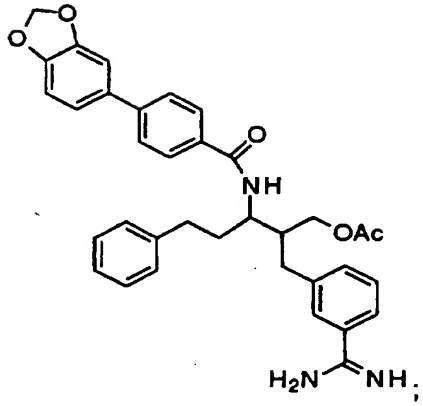
10

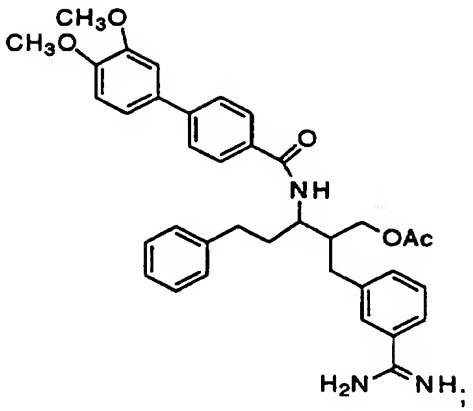












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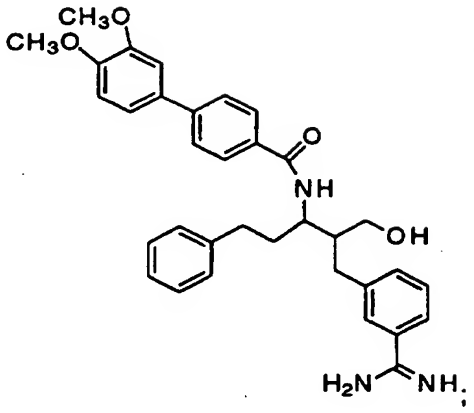

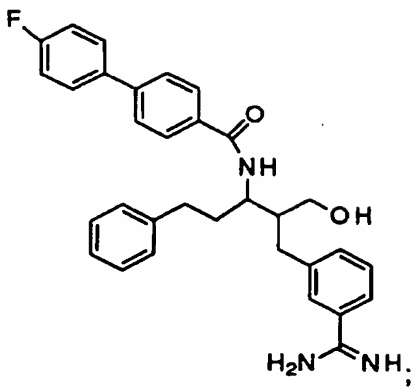

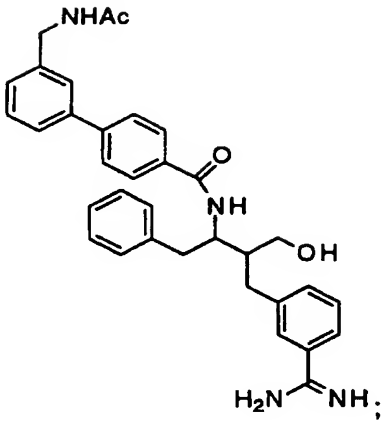

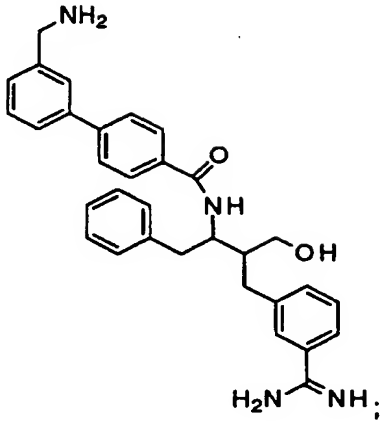

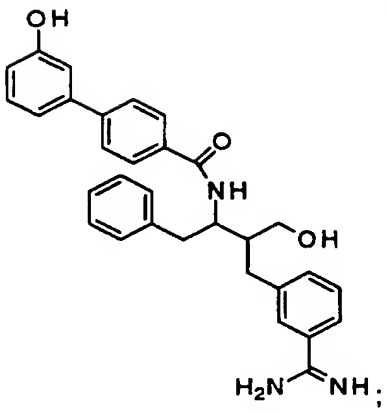

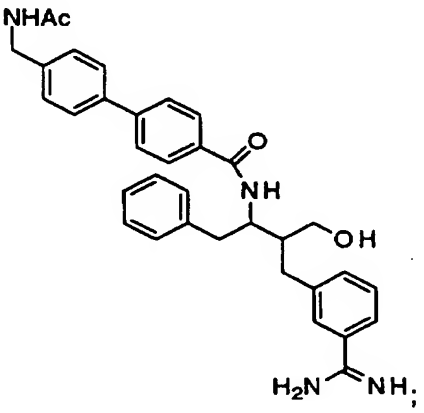

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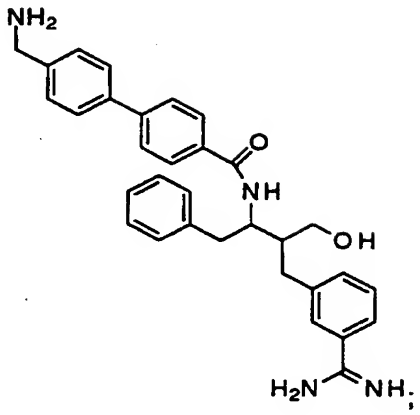

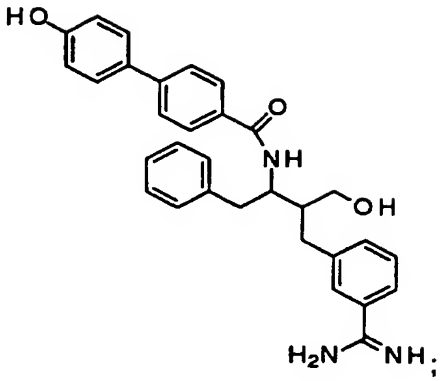

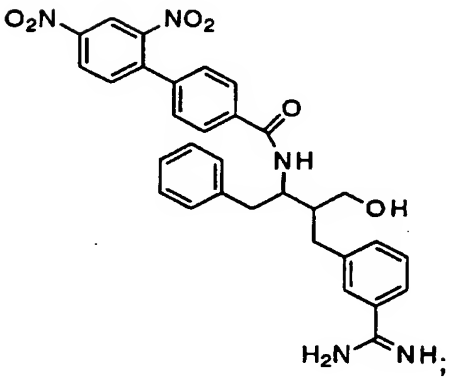

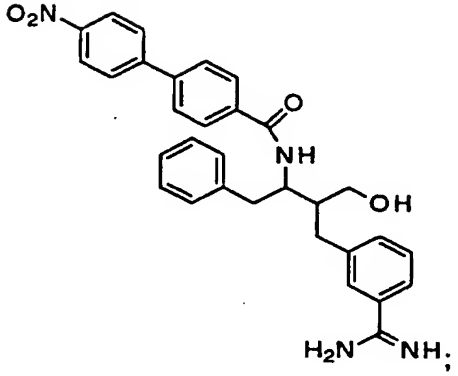

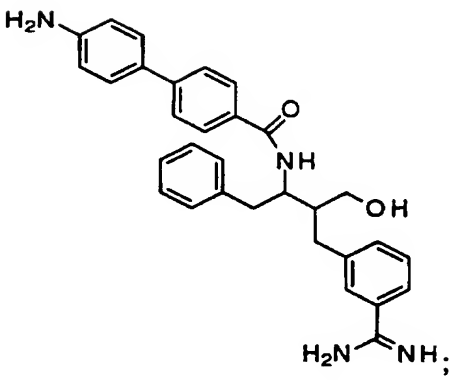

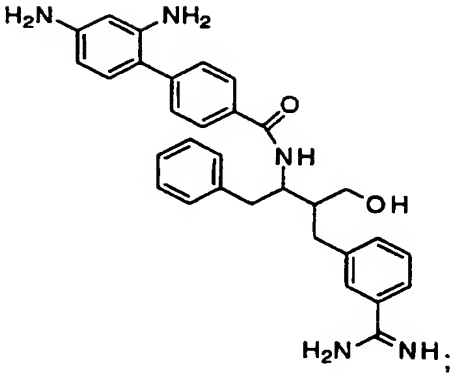

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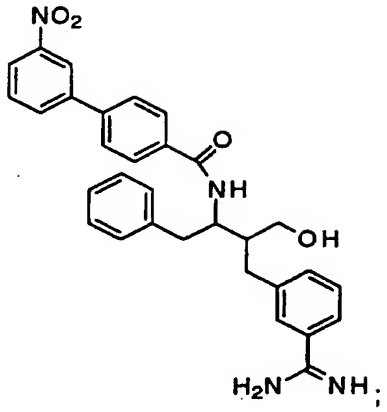
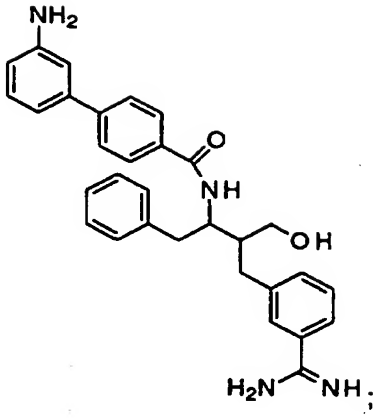
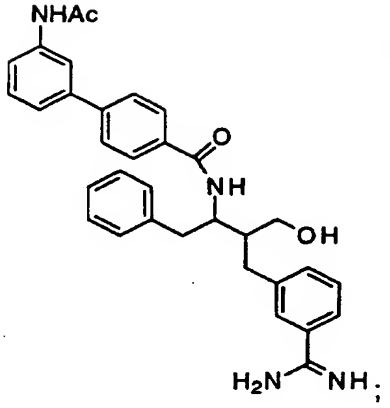
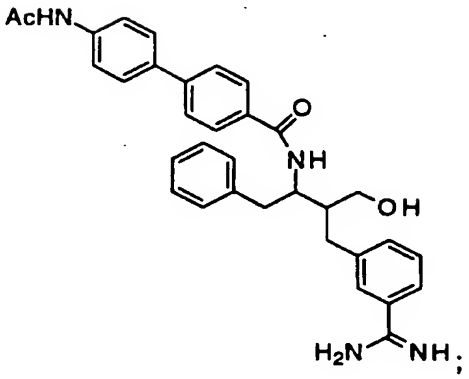
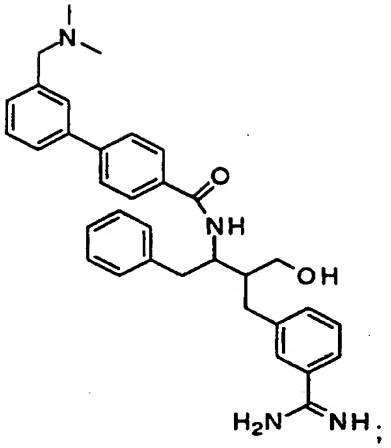
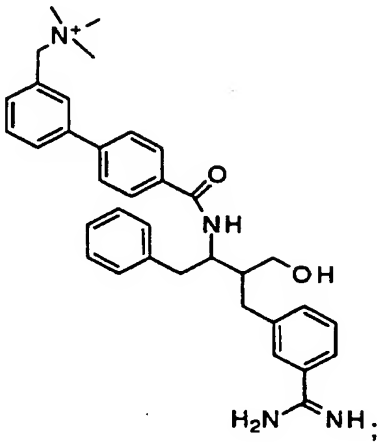

NO2
O
NH
OH
H2N
NH

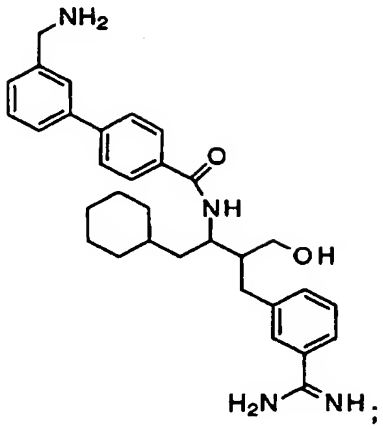

NH2
O
NH
OH
H2N
NH

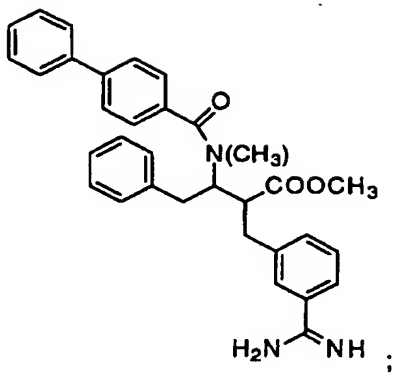

NHAc
O
NH
OH
H2N
NH

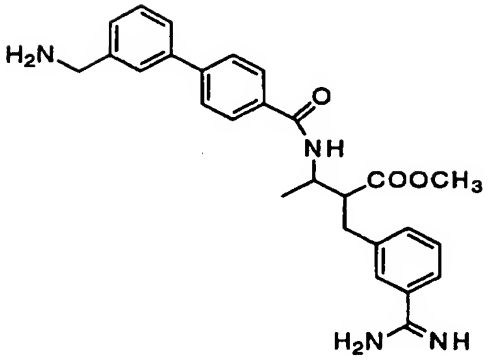

AcHN
O
NH
OH
H2N
NH

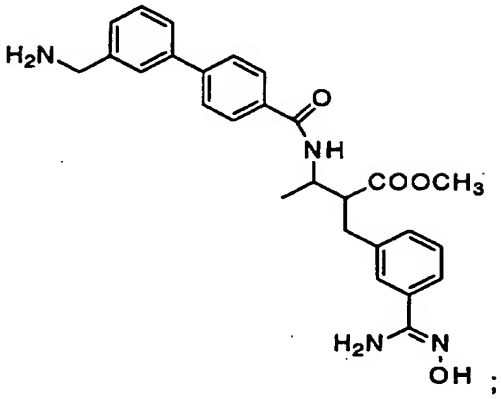

N
O
NH
OH
H2N
NH

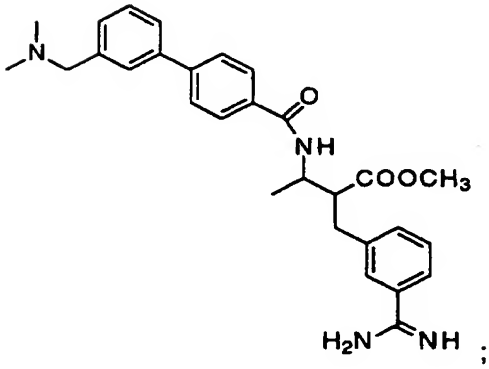

N+
O
NH
OH
H2N
NH

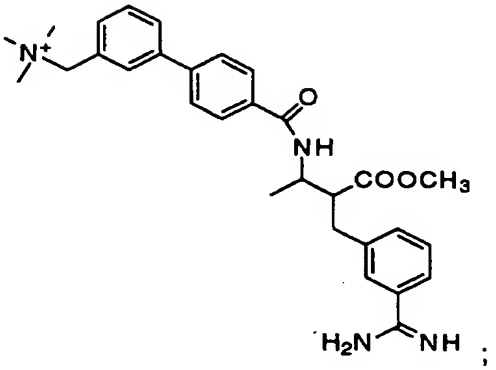












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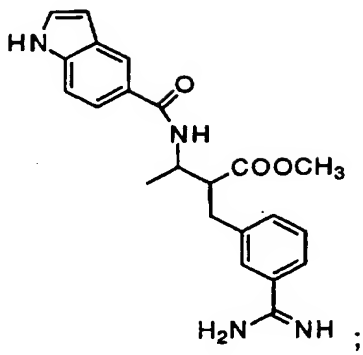
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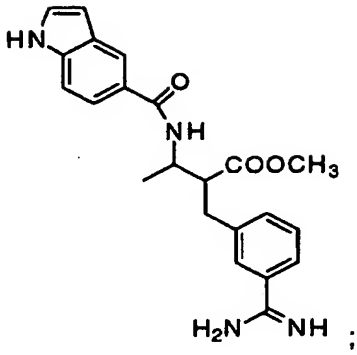
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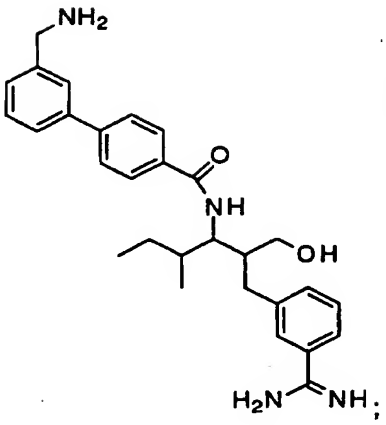
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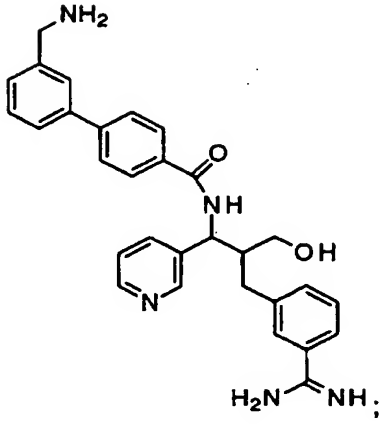
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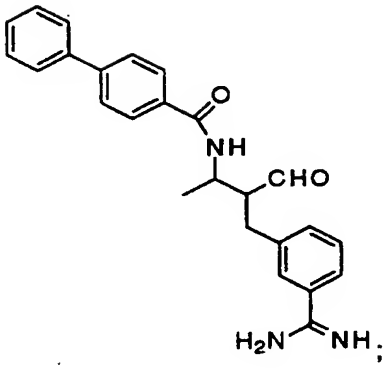
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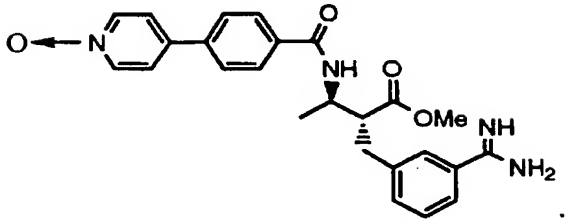
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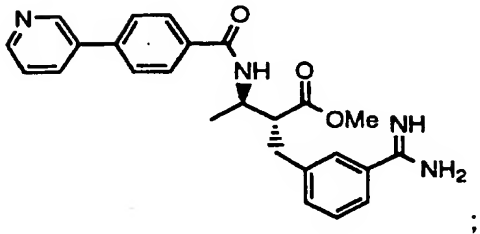
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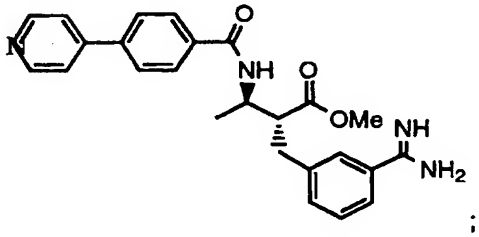
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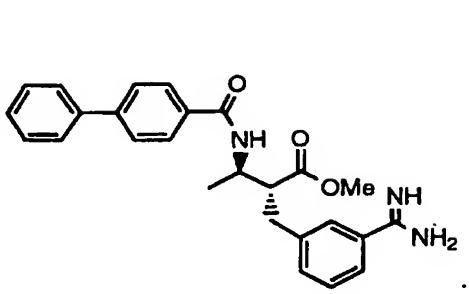
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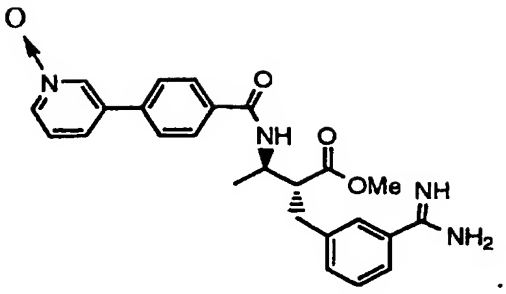
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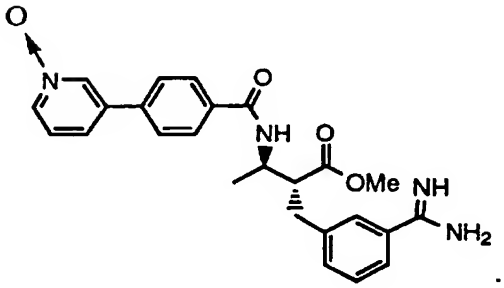
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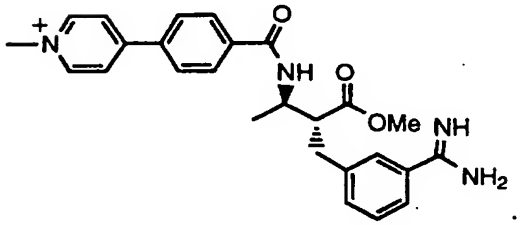
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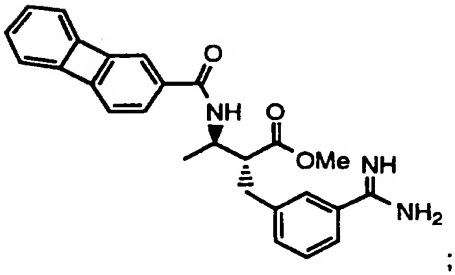
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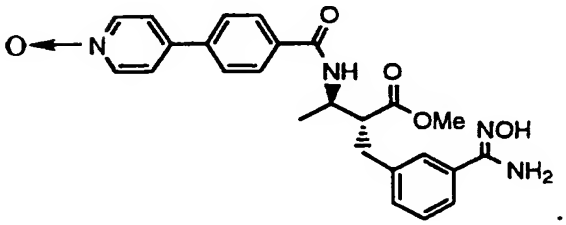
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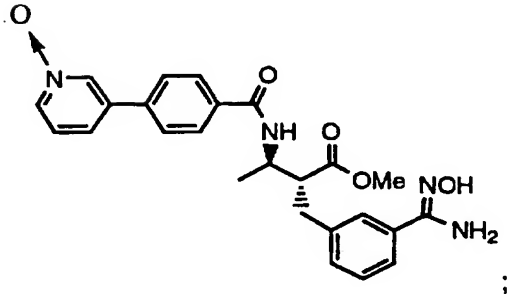
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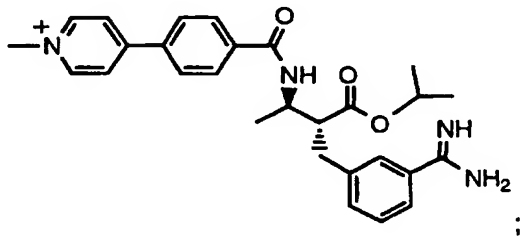
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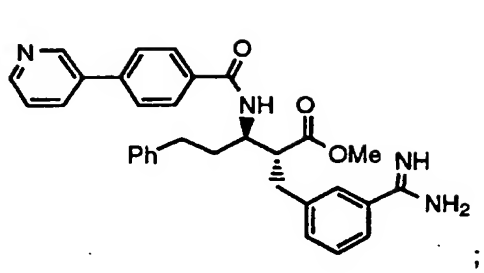

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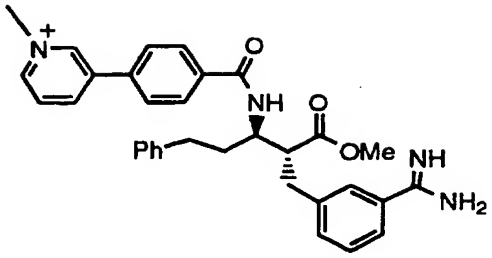

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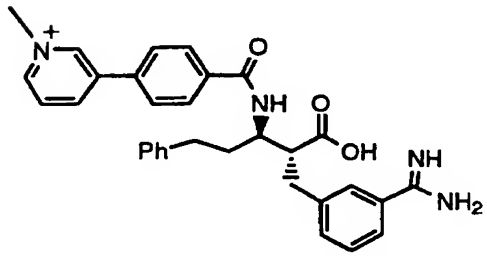

12. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method for treating a disease state capable of being modulated by inhibiting production of Factor Xa to a patient suffering from said disease state an effective amount of the compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20770

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/24, 31/195, 31/165; C07C 251/02, 205/06, 229/28, 233/64
US CL : 514/534, 563, 617; 560/22, 35; 562/440; 564/161, 163, 168, 169
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/534, 563, 617; 560/22, 35; 562/440; 564/161, 163, 168, 169

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,424,334 A (ABOOD, et al.) 13 June 1995, entire patent	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 APRIL 1997	Date of mailing of the international search report 25 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH M. CONRAD III Telephone No. (703) 308-4615

Form PCT/ISA/210 (second sheet)(July 1992)*